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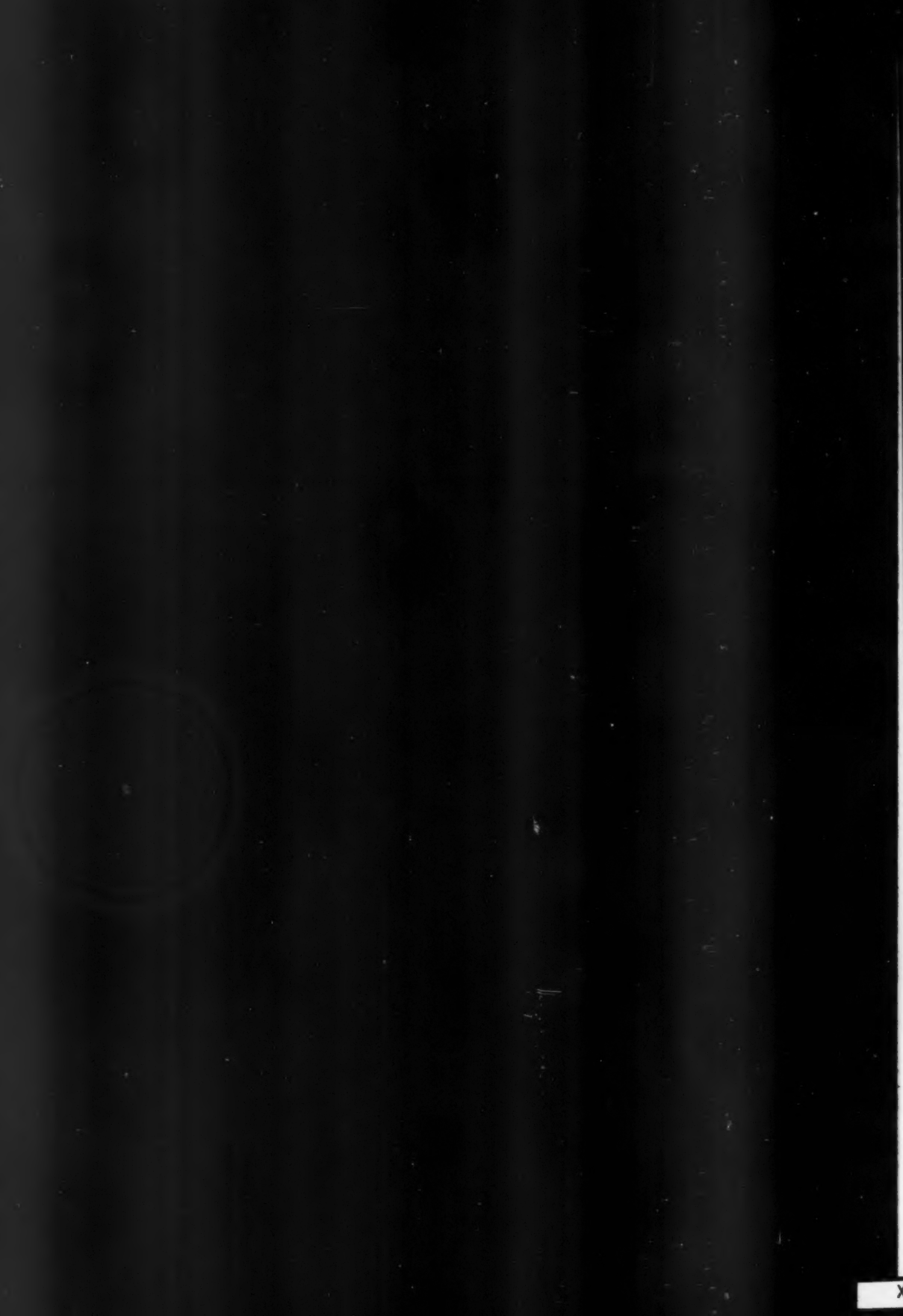
XUM



XUM

CONTENTS

General, physical, and inorganic

NO.		PAGE
98	Molecular complexes exhibiting polarization bonding. Part III. A structural survey of some aromatic complexes By S. C. WALLWORK	494
115	Cyclopentadienylnickel–acetylene complexes By J. F. TILNEY-BASSETT	577
119	Transition-metal complexes of seven-membered ring systems. Part III. Cycloheptatrieneiron carbonyl and related compounds By R. BURTON, L. PRATT, and G. WILKINSON	594
120	Some diolefincobalt carbonyl complexes By G. WINKHAUS and G. WILKINSON	602
121	Theoretical temperature-dependence of the rate of isomerization of cyclopropane By N. B. SLATER	606
122	The thermal isomerization of cyclopropane By W. E. FALCONER, T. F. HUNTER, and A. F. TROTMAN-DICKENSON	609
128	A convenient method for the preparation of [^{36}Cl]chlorine from [^{36}Cl]hydrochloric acid: decomposition of palladous [^{36}Cl]chloride By I. C. MCNEILL	639
139	The variation of bond type in cyclopentadienyl–metal compounds By DAVID A. BROWN	690
149	The structure of " cyclopropane platinous chloride " By D. M. ADAMS, J. CHATT, R. G. GUY, and N. SHEPPARD	738
	NOTES	
150	The nuclear magnetic resonance spectrum of *cis*-1,2-difluoroethylene By T. D. COYLE, S. L. STAFFORD, and F. G. A. STONE	743
156	Molybdenum(II) complexes containing triphenyl-phosphine oxide or -arsine oxide By J. C. SHELDON	750

Physical organic

97	Infrared spectra and structure of some 1,3-oxazine derivatives By Z. ECKSTEIN, P. GLUZIŃSKI, W. HOFMAN, and T. URBAŃSKI	489
100	An infrared spectroscopic investigation of nucleic acid constituents By C. L. ANGELL	504
107	Aromatic reactivity. Part XIV. Cleavage of aryltricyclohexyl- and aryltrimethyl-stannanes by aqueous-ethanolic perchloric acid By C. EABORN and J. A. WATERS	542
110	Homolytic aromatic substitution. Part XXI. The arylation of benzotrihalides By D. H. HEY, F. C. SAUNDERS, and GARETH H. WILLIAMS	554
111	Homolytic aromatic substitution. Part XXII. The esters formed in the reaction of benzoyl peroxide with aromatic solvents By D. I. DAVIES, D. H. HEY, and GARETH H. WILLIAMS	562
112	Homolytic aromatic substitution. Part XXIII. A redetermination of the relative rate of phenylation of nitrobenzene By D. H. HEY, S. ORMAN, and GARTH H. WILLIAMS	565
113	Physical properties and chemical constitution. Part XXXII. Thiophen compounds By G. H. JEFFERY, R. PARKER, and A. I. VOGEL	570
114	Competition between aniline and phenol for a triphenylmethyl cation By GABRIEL CHUCHANI	575

XUM

NO.		PAGE
126	Oxidations of organic compounds with quinquevalent vanadium. Part VII. The kinetic resemblance between the oxidations of some α-hydroxy-acids and that of pinacol and of its monomethyl ether By J. R. JONES, WILLIAM A. WATERS, and (in part) J. S. LITTLER	630
132	Infrared spectra of substituted salicylic acids and their esters By C. J. W. BROOKS, G. EGLINTON, and J. F. MORMAN	661
145	Kinetics of the bromination of ethyl malonate and methyl methanetricarboxylate By R. P. BELL and D. J. RAWLINSON	726
146	The cationic polymerization of styrene. Part I. The 1-phenylethyl cation By D. O. JORDAN and F. E. TRELOAR	729
147	The cationic polymerization of styrene. Part II. Spectra of polymerizing systems By D. O. JORDAN and F. E. TRELOAR	734
148	The cationic polymerization of styrene. Part III. The cocatalytic action of water in the polymerization of styrene by aluminium chloride By D. O. JORDAN and F. E. TRELOAR	737
NOTES		
158	Fission of triphenylmethyl derivatives of secondary cellulose acetates by hydrogen bromide By W. R. D. LEIGH	754
163	Deamination of cyclohexylamine by [^{18}O]nitrous acid By D. L. BOUTLE and C. A. BUNTON	761

Organic

99	Flavan derivatives. Part IV. Teracacidin, a new leucoanthocyanidin from *Acacia intertexta* By J. W. CLARK-LEWIS, G. F. KATEKAR, and P. I. MORTIMER	499
101	Diaryls. Part III. Reactions of some dihalogenonaphthalenes with lithium amalgam, and simple syntheses of 2,3:6,7-dibenzobiphenylene By E. R. WARD and B. D. PEARSON	515
102	1,2,4-Triazoles. Part II. 3-Alkyl-5-aryl-1,2,4-triazoles By D. R. LILJEGREN and K. T. POTTS	518
103	Alternaric acid. Part V. Biosynthesis By W. B. TURNER	522
104	Studies on specific chemical fission of peptide links. Part III. Fission of peptides containing one glutamic acid residue By A. R. BATTERSBY and J. J. REYNOLDS	524
105	The alkaline degradation of glucose and of some of its acetyl derivatives By W. M. CORBETT and A. MARGARET LIDDLE	531
106	The preparation of the geraniolenes By M. F. ANSELL and D. A. THOMAS	539
108	Dicyclopentadienyl-tin and -lead By H. P. FRITZ and E. O. FISCHER	547
109	A new triterpene from the Hong Kong Ericaceae: an epoxyglutinane from *Rhododendron westlandii* By H. R. ARTHUR and (MISS) W. H. HUI	551
116	A bisglycerol tricarbonate By L. HOUGH and J. E. PRIDDLE	581
117	Diazaindenes and their quaternary salts. Part II. The cyclisation of isopropyl methyl ketone 3-pyridylhydrazone By G. E. FICKEN and J. D. KENDALL	584
118	Some isomeric amido- and amino-derivatives of 9-methyl- and 9,10-dimethyl-anthracene By A. H. BECKETT and R. G. LINGARD	588
123	Optical studies of 2,2′-di-t-butylbiphenylcarboxylic acids and of 2′-t-butylbiphenyl-2-carboxylic acid By MARY S. LESLIE and URSULA J. H. MAYER	611

NO.		PAGE
124	Some reactions of tributyl- and triphenyl-stannyl derivatives of alkali metals By D. BLAKE, G. E. COATES, and J. M. TATE	618
125	The structure of isolichenin By STANLEY PEAT, W. J. WHELAN, J. R. TURVEY, and K. MORGAN	623
127	Parmacodynamic compounds. Part II. Some rearrangements in the pyrrolidine–piperidine series By E. G. BRAIN, F. P. DOYLE, and M. D. MEHTA	633
129	Constituents of *Eugenia maire* A. Cunn. Part I. A trimethyl ether of ellagic acid and mairin, a new triperpene By LINDSAY H. BRIGGS, R. C. CAMBIE, J. B. LOWRY, and R. N. SEELYE	642
130	The chemistry of triterpenes and related compounds. Part XXXVIII. The acidic constituents of dammar resin By S. BREWIS and T. G. HALSALL	646
131	The synthesis of some thiophens related to vitamin A By R. M. ACHESON, J. A. BARLTROP, M. HICHENS, and R. E. HICHENS	650
133	The synthesis of chelating agents related to cyclohexane-1,2-diamine-*NNN'N'*-tetra-acetic acid By R. BELCHER, W. HOYLE, and T. S. WEST	667
134	Olefinic additions with asymmetric reactants. Part VI. Dissymmetric hydrogenation of (±)-4-phenylpent-3-en-2-ol By C. L. ARCUS and T. J. HOWARD	670
135	The structure of 1,5-diketones By I. L. FINAR	674
136	The reaction between *N*-methyldi-(2-chloroethyl)amine and thiosulphate By E. BOYLAND and R. NERY	679
137	The kinetics and mechanism of carbonyl–methylene condensation reactions. Part XI. Stereochemistry of the products By JACOB ZABICKY	683
138	The kinetics and mechanism of carbonyl–methylene condensation reactions. Part XII. The elimination step of the uncatalysed condensation in water By JACOB ZABICKY	687
140	The chemistry of extractives from hardwoods. Part XXXI. 2-Acetyl-1,8-dihydroxy-3-methylnaphthalene (musizin), a constituent of *Maesopsis eminii* By C. J. COVELL, F. E. KING, and J. W. W. MORGAN	702
141	β-Aroylpropionic acids. Part XVIII. Their conversion into 4,5-diarylfuran-2,3-dicarboxylic acids By F. G. BADDAR and SAYED SHERIF	707
142	The oxidation of cyclic phosphites to cyclic phosphates By L. KEAY and E. M. CROOK	710
143	Studies on phosphorylation. Part XXII. Phosphorylation accompanying the oxidation of quinol phosphates By V. M. CLARK, D. W. HUTCHINSON, G. W. KIRBY, and SIR ALEXANDER TODD	715
144	Studies on phosphorylation. Part XXIII. Oxidative phosphorylation leading to adenosine-5′ pyrophosphate By V. M. CLARK, D. W. HUTCHINSON, and SIR ALEXANDER TODD	722

NOTES

151	Nitroethylene and some indolylmagnesium iodides By R. M. ACHESON and A. R. HANDS	744
152	5-Hydroxyskatole By R. M. ACHESON and A. R. HANDS	746
153	So-called " 2-triacetylthiophen " (a boron compound) By G. M. BADGER and JENNETH M. SASSE	746
154	2,3-Dihydro-3,3-dimethyl-1H-1,7-diazaindan-2-one By G. E. FICKEN and J. D. KENDALL	747
155	2,4′-Diphenylbiphenyl [*op*′-quaterphenyl] By D. H. HEY, M. J. PERKINS, and GARETH H. WILLIAMS	748

XUM

NO.		PAGE
157	Sandaraco- and crypto-pimaric acid By J. W. Apsimon, B. Green, and W. B. Whalley	752
159	8-Hydroxyquinoline complexes of the dibutyl- and diphenyl-tin radicals By D. Blake, G. E. Coates, and J. M. Tate	756
160	Further studies on the preparation of symmetrical pinacols by cathodic reduction By M. J. Allen, M. Cohen, W. G. Pierson, and (Miss) J. A. Siragusa	757
161	Quaternary derivatives of 2,2′-pyridil dioxime and of 2,2′-bipyridyls By Mary Pitman and P. W. Sadler	759
162	A simple route to 4,5-diamino-2-hydroxypyrimidine By Abraham Kalmus and Felix Bergmann	760
164	An enzymic resolution of serine By Leo Benoiton	763

INDEX OF AUTHOR'S NAMES

Acheson, R. M., Barltrop, J. A., Hichens, M., and Hichens, R. E., 650
Acheson, R. M., and Hands, A. R., 744, 746
Adams, D. M., Chatt, J., Guy, R. G., and Sheppard, N., 738
Allen, M. J., Cohen, M., Pierson, W. G., and Siragusa, J. A., 757
Angell, C. L., 504
Ansell, M. F., and Thomas, D. A., 539
Apsimon, J. W., Green, B., and Whalley, W. B., 752
Arcus, C. L., and Howard, T. J., 670
Arthur, H. R., and Hui, W. H., 551
Baddar, F. G., and Sherif, S., 707
Badger, G. M., and Sasse, J. M., 746
Barltrop, J. A. See Acheson, R. M., 650
Battersby, A. R., and Reynolds, J. J., 524
Beckett, A. H., and Lingard, R. G., 588
Belcher, R., Hoyle, W., and West, T. S., 667
Bell, R. P., and Rawlinson, D. J., 726
Benoiton, L., 763
Bergmann, F. See Kalmus, A., 760
Blake, D., Coates, G. E., and Tate, J. M., 618, 756
Boutle, D. L., and Bunton, C. A., 761
Boyland, E., and Nery, R., 679
Brain, E. G., Doyle, F. P., and Mehta, M. D., 633
Brewis, S., and Halsall, T. G., 646
Briggs, L. H., Cambie, R. C., Lowry, J. B., and Seelye, R. N., 642
Brooks, C. J. W., Eglinton, G., and Morman, J. F., 661
Brown, D. A., 690
Bunton, C. A. See Boutle, D. L., 761
Burton, R., Pratt, L., and Wilkinson, G., 594
Cambie, R. C. See Briggs, L. H., 642
Chatt, J. See Adams, D. M., 738
Chuchani, G., 575
Clark, V. M., Hutchinson, D. W., Kirby, G. W., and Todd, Sir A., 715
Clark, V. M., Hutchinson, D. W., and Todd, Sir A., 722
Clark-Lewis, J. W., Katekar, G. F., and Mortimer, P. I., 499
Coates, G. E. See Blake, D., 618, 756
Cohen, M. See Allen, M. J., 757
Corbett, W. M., and Liddle, A. M., 531
Covell, C. J., King, F. E., and Morgan, J. W. W., 702
Coyle, T. D., Stafford, S. L., and Stone, F. G. A., 743
Crook, E. M. See Keay, L., 710
Davies, D. I., Hey, D. H., and Williams, G. H., 562
Doyle, F. P. See Brain, E. G., 633
Eaborn, C., and Waters, J. A., 542
Eckstein, Z., Gluziński, P., Hofman, W., and Urbański, T., 489
Eglinton, G. See Brooks, C. J. W., 661
Falconer, W. E., Hunter, T. F., and Trotman-Dickenson, A. F., 609
Ficken, G. E., and Kendall, J. D., 584, 747
Finar, I. L., 674
Fischer, E. O. See Fritz, H. P., 547
Fritz, H. P., and Fischer, E. O., 547
Gluziński, P. See Eckstein, Z., 489
Green, B. See Apsimon, J. W., 752
Guy, R. G. See Adams, D. M., 738
Halsall, T. G. See Brewis, S., 646
Hands, A. R. See Acheson, R. M., 744, 746
Hey, D. H., Orman, S., and Williams, G. H., 565
Hey, D. H., Perkins, M. J., and Williams, G. H., 748
Hey, D. H., Saunders, F. C., and Williams, G. H., 554
Hey, D. H. See also Davies, D. I., 562
Hichens, M. See Acheson, R. M., 650
Hichens, R. E. See Acheson, R. M., 650
Hofman, W. See Eckstein, Z., 489
Howard, T. J. See Arcus, C. L., 670
Hough, L., and Priddle, J. E., 581
Hoyle, W. See Belcher, R., 667
Hui, W. H. See Arthur, H. R., 551
Hunter, T. F. See Falconer, W. E., 609
Hutchinson, D. W. See Clark, V. M., 715, 722
Jeffery, G. H., Parker, R., and Vogel, A. I., 570
Jones, J. R., Waters, W. A., and Littler, J. S., 630
Jordan, D. O., and Treloar, F. E., 729, 734, 737
Kalmus, A., and Bergmann, F., 760
Katekar, G. F. See Clark-Lewis, J. W., 499
Keay, L., and Crook, E. M., 710
Kendall, J. D. See Ficken, G. E., 584, 747
King, F. E. See Covell, C. J., 702
Kirby, G. W. See Clark, V. M., 715
Leigh, W. R. D., 754
Lesslie, M. S., and Mayer, U. J. H., 611
Liddle, A. M. See Corbett, W. M., 531
Liljegren, D. R., and Potts, K. T., 518
Lingard, R. G. See Beckett, A. H., 588
Littler, J. S. See Jones, J. R., 630

Lowry, J. B. See Briggs, L. H., 642
McNeill, I. C., 639
Mayer, U. J. H. See Lesslie, M. S., 611
Mehta, M. D. See Brain, E. G., 633
Morgan, J. W. W. See Covell, C. J., 702
Morgan, K. See Peat, S., 623
Morman, J. F. See Brooks, C. J. W., 661
Mortimer, P. I. See Clark-Lewis, J. W., 499
Nery, R. See Boyland, E., 679
Orman, S. See Hey, D. H., 565
Parker, R. See Jeffery, G. H., 570
Pearson, B. D. See Ward, E. R., 515
Peat, S., Whelan, W. J., Turvey, J. R., and Morgan, K., 623
Perkins, M. J. See Hey, D. H., 748
Pierson, W. G. See Allen, M. J., 757
Pitman, M., and Sadler, P. W., 759
Potts, K. T. See Liljegren, D. R., 518
Pratt, L. See Burton, R., 594
Priddle, J. E. See Hough, L., 581
Rawlinson, D. J. See Bell, R. P., 726
Reynolds, J. J. See Battersby, A. R., 524
Sadler, P. W. See Pitman, M., 759
Sasse, J. M. See Badger, G. M., 746
Saunders, F. C. See Hey, D. H., 554
Seelye, R. N. See Briggs, L. H., 642
Sheldon, J. C., 750
Sheppard, N. See Adams, D. M., 738
Sherif, S. See Baddar, F. G., 707
Siragusa, J. A. See Allen, M. J., 757
Slater, N. B., 606
Stafford, S. L. See Coyle, T. D., 743
Stone, F. G. A. See Coyle, T. D., 743
Tate, J. M. See Blake, D., 618, 756
Thomas, D. A. See Ansell, M. F., 539
Tilney-Bassett, J. F., 577
Todd, Sir A. See Clark, V. M., 715, 722
Treloar, F. E. See Jordan, D. O., 729, 734, 737
Trotman-Dickenson, A. F. See Falconer, W. E., 609
Turner, W. B., 522
Turvey, J. R. See Peat, S., 623
Urbański, T. See Eckstein, Z., 489
Vogel, A. I. See Jeffery, G. H., 570
Wallwork, S. C., 494
Ward, E. R., and Pearson, B. D., 515
Waters, J. A. See Eaborn, C., 542
Waters, W. A. See Jones, J. R., 630
West, T. S. See Belcher, R., 667
Whalley, W. B. See Apsimon, J. W., 752
Whelan, W. J. See Peat, S., 623
Wilkinson, G. See Burton, R., 594, and Winkhaus, G., 602
Williams, G. H. See Davies, D. I., 562, and Hey, D. H., 554, 565, 748
Winkhaus, G., and Wilkinson, G., 602
Zabicky, J., 683, 687

XUM

PAPERS ACCEPTED

Synthesis of peptidyl-nucleotidates including L-arginyl-L-alanyl-L-arginyl-L-alanyluridine-5′ phosphate. By G. HARRIS and I. C. MACWILLIAM

Ruthenium red. By J. M. FLETCHER, B. F. GREENFIELD, C. J. HARDY, and J. L. WOODHEAD

Solvent-extraction of septivalent rhenium. Part I. Heterogeneous equilibria in the system aqueous nitric acid–potassium perrhenate–tributyl phosphate. By A. S. KERTES and A. BECK

Solvent-extraction of septivalent rhenium. Part II. Heterogeneous equilibria in the system aqueous nitric acid–potassium perrhenate–tris-(2,2,4-trimethylpentyl)amine. By A. S. KERTES and A. BECK

Poly-*p*-xylylene and related polymers. By J. H. GOLDEN

Metal complexes of bis-[3-di(carboxymethyl)aminopropyl] ether. The computation of stability constants with the aid of a high-speed digital computor. By H. IRVING and M. H. STACEY

The dissociation constants of some chlorides and perchlorates in aqueous acetone from conductance measurements. By V. M. ATKINS and C. B. MONK

The adsorption of uranyl sulphate from 20% methanol by an anion-exchange resin. By D. E. B. MORGANS and C. B. MONK

Modified steroid hormones. Part XXI. 11-Methylene and 11β-methylandrostanolones. By D. N. KIRK and V. PETROW

The nucleotide sequence in deoxyribonucleic acids. Part V. The alkaline degradation of apurinic acids. By C. R. BAYLEY, K. W. BRAMMER, and A. S. JONES

Sulphur chloride pentafluoride: reaction with unsaturated hydrocarbons. By J. R. CASE, N. H. RAY, and H. L. ROBERTS

The thermodynamic properties of organic oxygen compounds. Part II. Vibrational assignment and calculated thermodynamic properties of phenol. By J. H. S. GREEN

The nature of the Porter–Silber reaction. By D. H. R. BARTON, T. C. MCMORRIS, and R. SEGOVIA

Biformene. By R. M. CARMAN and P. K. GRANT

Sulphur chloride pentafluorides: reaction with fluoro-olefines. By J. R. CASE, N. H. RAY, and H. L. ROBERTS

Studies of trifluoroacetic acid. Part XVIII. The reaction of *N*-aroylglycines with perfluorocarboxylic anhydrides. By E. J. BOURNE, J. BURDON, V. C. R. MCLOUGHLIN, and J. C. TATLOW

The reaction between acetimidoyl esters and acid ester of phosphoric acid. By R. J. W. CREMLYN

Compounds related to the steroid hormones. Part II. The action of hydrogen bromide on 2-bromo-3-oxo-Δ^1-5α-steroids. By F. G. H. GREEN and A. G. LONG

The ultraviolet absorption of isolated double bonds. By J. H. CHAPMAN and A. C. PARKER

Conformation and reactivity. Part III. Kinetics of the acid-catalysed hydrolysis of the methyl cyclohexane-mono- and -di-carboxylates and 4-t-butylcyclohexanecarboxylates. By N. B. CHAPMAN, J. SHORTER, and K. J. TOYNE

The crystal and molecular structure of (+)-10-bromo-2-chloro-2-nitrosocamphane. By G. FERGUSON, C. J. FRITCHIE, J. MONTEATH ROBERTSON, and G. A. SIM

Heterocyclic derivatives of guanidine. Part II. Some derived products. By J. E. BANFIELD

The chemotherapy of schistosomiasis. Part IV. Some ethers of 4-amino-2-methoxyphenol. By R. F. COLLINS and M. DAVIS

Stability constants of some metal complexes of *ortho*-aminophenols. By D. D. PERRIN

The infrared spectra of some oxamides and thio-oxamides. By BRIAN MILLIGAN, E. SPINNER, and J. M. SWAN

Rearrangement of sulphonhydrazides. By P. CARTER and T. S. STEVENS

Dinitrogen trioxide. Part IV. Composition of the vapour in equilibrium with liquid mixtures of nitrogen dioxide and nitric oxide. By I. R. BEATTIE and A. J. VOSPER

The vapour pressure of PuF_4. By C. J. MANDLEBERG and D. DAVIES

Transition metal complexes of seven-membered ring systems. Part IV. Proton resonance spectra of cycloheptatriene complexes of Group VI metals. By M. A. BENNETT, L. PRATT, and G. WILKINSON

Electron donor and acceptor complexes with aromatic systems. Part VI. Complexes of monocyclic aromatic molecules. By N. D. PARKYNS and A. R. UBBELOHDE

XUM

Chemical and magnetic properties of lanthanum dicarbide and sesquicarbide. By N. N. GREENWOOD and A. J. OSBORN

The preparation and properties of chelated sulphatebis(ethylenediamine) cobalt(III) salts. By C. G. BARRACLOUGH and M. L. TOBE

Thermodynamic properties of organic oxygen compounds. Part III. Formic acid. By J. H. S. GREEN

Mechanism of substitution of chlorine in *cis*- and *trans*-chloronitrobis(ethylenediamine)-cobalt(III) ions with thiocyanate in methanol solution. By S. ASPERGER, D. PAVLOVIC, and M. ORHANOVIC

Gallotannins. Part I. Introduction and the fractionation of tannase. By E. HASLAM, R. D. HAWORTH, K. JONES, and H. J. ROGERS

Gallotannins. Part II. Some esters and depsides of gallic acid. By E. HASLAM, R. D. HAWORTH, S. D. MILLS, H. J. ROGERS, and (in part) R. ARMITAGE, and T. SEARLE

Gallotannins. Part III. The constitution of Chinese, Turkish sumach, and tara tannins. By R. ARMITAGE, G. S. BAYLISS, J. W. CRAMSHAW, E. HASLAM, R. D. HAWORTH, K. JONES, H. J. ROGERS, and T. SEARLE

Gallotannins. Part IV. The biosynthesis of gallic acid. By E. HASLAM, R. D. HAWORTH, and P. F. KNOWLES

The isolation of festuclavine and two new clavine alkaloids from *Aspergillus fumigatus* fres. By J. F. SPILSBURY and S. WILKINSON

Basic tin(II) nitrate. By J. D. DONALDSON and V. MOSER

The mechanism of epoxide reactions. Part III. The reactions of *p*-bromo(1,2-epoxyethyl)-benzene and *p*-(1,2-epoxyethyl)toluene with benzylamine. By J. K. ADDY, R. M. LAIRD, and R. E. PARKER

The hydrogen bonding of imidazole in carbon tetrachloride solution. By D. M. W. ANDERSON, J. L. DUNCAN, and F. J. C. ROSSOTTI

The kinetics of complex-formation of *s*-trinitrobenzene with diethylamine and other amines in solution at low temperatures. By G. R. ALLEN, A. J. BROOK, and E. F. CALDIN

Ethylene–platinous chloride pyridine *N*-oxide. By LEONARDO GARCIA and MILTON ORCHIN

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97. *Infrared Spectra and Structure of Some 1,3-Oxazine Derivatives.*

By Z. Eckstein, P. Gluziński, W. Hofman, and T. Urbański.

Molecular refractivities and infrared absorption spectra have been determined for a number of 3,5-dialkyltetrahydro-5-nitro-1,3-oxazines, as well as for some analogues without nitro-groups (a total of 24 substances).

Values of $[M]_D$ were lower than those calculated, which is explained as due to the influence of the heteroatoms in the ring.

Infrared bands in the regions 1150—1050, 955—925, and 855—800 cm.$^{-1}$ are now assigned to C–O–C acetal bonds, which confirm the acetal character of 1,3-oxazines. Probable assignments have been made for the various carbon–nitrogen bonds.

One of the characteristics of tetrahydro-5-nitro-1,3-oxazines [1] is hydrolysis in an acid medium, with the loss of one molecule of formaldehyde, to derivatives of 3-amino-2-nitropropan-1-ol. This occurs readily under the action of hydrochloric acid in 80% ethanol [2] or of concentrated hydrochloric acid under ultraviolet irradiation.[3] The ease of this reaction suggested that the C–O–C bond in 1,3-oxazines was mainly of hemiacetal character.[4]

To prove finally the cyclic structure of these compounds and to confirm the nature of the C–O–C bond the molecular refractivities and infrared absorption spectra of a few compounds of type (I) have now been investigated. A few absorption spectra of 1,3-oxazine derivatives have been published,[5] but there has been no previous systematic investigation.

The products (I; R = Me or Et) were prepared by condensing nitroethane and 1-nitropropane respectively with formaldehyde and treating the resulting 1,3-diols with formaldehyde and primary amines ranging from ammonia to hexylamine. Particular attention was paid to the purity of the products (I): they were distilled under reduced pressure, cyrstallised as hydrochlorides, recovered as bases and redistilled under reduced pressure.

For comparison, a few 1,3-oxazines without the nitro-group were also investigated, namely, (II) [6] and the 5,6-dihydro-oxazine (III).[7]

Experimental

3,5-Dimethyltetrahydro-5-nitro-1,3-oxazine, prepared from 2-methyl-2-nitropropane-1,3-diol, formaldehyde, and methylamine as described by Senkus [1] (yield 85·4%), had b. p. 85—86°/0·7 mm.

3-*Ethyltetrahydro-5-methyl-5-nitro*-1,3-*oxazine*. 2-Methyl-2-nitropropane-1,3-diol (0·2 mol., 27 g.) (prepared from nitroethane and formaldehyde) was dissolved in 60% aqueous ethylamine (0·2 mol., 15 g.) and mixed with 30% aqueous formaldehyde (0·2 mol., 20 ml.). The temperature rose by 55° and, after cooling, the whole was kept at room temperature for 48 hr. The colourless oily oxazine was extracted with ether, dried (Na_2SO_4), freed from ether and volatile substances on water-bath, and distilled under reduced pressure (101—103°/3 mm.) as a colourless oil which slowly darkened (28·6 g., 81·8%). This was treated in anhydrous alcohol with

[1] Hirst, Jones, Minahan, Ochynski, Thomas, and Urbański, *J.*, 1947, 924; U.S.P. 2,447,822; Senkus, *J. Amer. Chem. Soc.*, 1950, **72**, 2968; Urbański, *Nature*, 1951, **168**, 562; Urbański and Lipska, *Roczniki Chem.*, 1952, **26**, 182; Urbański and Gürne, *ibid.*, 1954, **28**, 175; Urbański and Piotrowska, *ibid.*, 1955, **29**, 379; Urbański and Kolesińska, *ibid.*, 1955, **29**, 392; Urbański, Dabrowska, Lesiowska, and Piotrowska, *ibid.*, 1957, **31**, 855.

[2] Eckstein, Sobótka, and Urbański, *Roczniki Chem.*, 1956, **30**, 132.

[3] Gürne and Urbański, *Roczniki Chem.*, 1957, **31**, 855; *ibid.*, 1957, **31**, 869; *J.*, 1959, 1912.

[4] Urbański, *Roczniki Chem.*, 1951, **25**, 257.

[5] Bergmann and Kaluszyner, *Rec. Trav. chim.*, 1959, **78**, 315; O'Sullivan and Sadler, *J.*, 1957, 2916; Urbański, *Roczniki Chem.*, 1958, **32**, 241; Lacey and Ward, *J.*, 1958, 2134; Lynn, *J. Org. Chem.*, 1959, **24**, 711.

[6] Kohn, *Monatsh.*, 1904, **25**, 817; Urbański and Gac-Chylińska, *Roczniki Chem.*, 1956, **30**, 185.

[7] Eckstein, Majewski, and Gluziński, unpublished work.

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alcoholic hydrochloric acid at 0°. The precipitated hydrochloride was washed with acetone, suspended in ether, and shaken with sodium hydrogen carbonate solution. The ethereal layer was dried and the free *oxazine* was distilled 84—85°/0·2 mm. (Found: N, 16·4. $C_7H_{14}O_3N_2$ requires N, 16·1%).

The other *oxazines* listed in Table 1 were similarly prepared from 2-methyl- or 2-ethyl-2-nitropropane-1,3-diol.

Refractivities were determined by means of Zeiss–Abbé model G refractometer at 20°. The calculated molecular refractivities are recorded in Table 2.

TABLE 1. *3,5-Dialkyltetrahydro-5-nitro-1,3-oxazines.*

3-Subst.	Yield (%)	B. p./mm.	Formula	N (%) Found	N (%) Reqd.
5-Methyl derivatives					
Pr^n	64	94°/0·3	$C_8H_{16}O_3N_2$	14·7	14·9
Pr^i [a]	68	98—99°/0·8	—	—	—
Bu^n	59	92—94°/0·2	$C_9H_{18}O_3N_2$	14·2	13·85
n-Pentyl	36	100—101°/0·2	$C_{10}H_{20}O_3N_2$	13·2	12·95
n-Hexyl [b]	60	141—142°/2·2	$C_{11}H_{22}O_3N_2$	11·9	12·2
5-Ethyl derivatives					
H [c]	—	108—109°/1	—	—	—
Me	75·5	100—101°/1·2	$C_7H_{14}O_3N_2$	16·4	16·1
Et	87	98—99°/0·7	$C_8H_{16}O_3N_2$	15·2	14·9
Pr^n	70	103—105°/0·6	$C_9H_{18}O_3N_2$	13·7	13·85
Pr^i	79	103—105°/0·1	,,	14·2	13·85
Bu^n [a]	57	111—112°/0·2	—	—	—
n-Pentyl	48	116—117°/0·4	$C_{11}H_{22}O_3N_2$	12·1	12·2
n-Hexyl [b]	47	129—130°/0·25	$C_{12}H_{24}O_3N_2$	11·8	11·5

[a] Cf. Senkus.[1] [b] Sufficient ethanol was added to give a homogeneous solution. [c] Cf. Hirst *et al.*[1]

TABLE 2. *Molecular refractivities of compounds* (I).

R	R′	d_{20}^{20}	n_D^{20}	$[M]_D$ Calc.*	$[M]_D$ Found	$\Delta[M]_D$
Me	Me	1·1698	1·4725	38·89	38·38	0·51
Me	Et	1·1314	1·4700	43·54	42·96	0·58
Me	Pr^n	1·0984	1·4679	48·21	47·62	0·59
Me	Pr^i	1·1081	1·4718	48·22	47·54	0·68
Me	Bu^n	1·0698	1·4671	52·83	52·46	0·37
Me	n-Pentyl	1·0547	1·4666	57·49	56·84	0·65
Me	n-Hexyl	1·0394	1·4669	62·10	61·46	0·64
Et	H	1·2051	1·4816	38·76	37·87	0·89
Et	Me	1·1377	1·4731	43·54	42·94	0·60
Et	Et	1·1030	1·4704	48·19	47·64	0·55
Et	Pr^n	1·0862	1·4702	52·86	51·97	0·89
Et	Pr^i	1·0884	1·4721	52·87	52·04	0·83
Et	Bu^n	1·0579	1·4694	57·48	56·98	0·50
Et	n-Pentyl	1·0419	1·4687	62·14	61·51	0·63
Et	n-Hexyl	1·0285	1·4689	66·75	66·14	0·61

* The refractivity increments used in calculating $[M]_D$ were $-CH_2-$ 4·647; C 2·59; tert.-N 2·74; sec.-NH 3·61; $-O-$ (as in acetals) 1·61; NO_2 aliph. 6·71; Me 5·65; Et 10·30; Pr^n 14·97; Pr 14·98; Bu^n 19·59; n-pentyl 24·25; n-hexyl 28·86.

Infrared absorption spectra were determined by means of a Hilger H-800 double-beam spectrophotometer with 60° prism of sodium chloride. Substances were used as liquids of capillary thickness. The frequencies were checked by means of a polystyrene film. The frequencies are recorded in Tables 3—5.

DISCUSSION

Molecular Refractivities.—Experimental values of the molecular refractivity were found to be lower than the calculated values ($\Delta[M]_D$ 0·4—0·9), as already noted by Bergmann and Kaluszyner [5] for tetrahydro-1,3-oxazine derivatives without the nitro-group. Small (three- and four-membered) and large (seven- and eight-membered) rings are sometimes

TABLE 3. *Infrared frequencies (cm.$^{-1}$) for compounds* (1).

Me	Me	Et	Et	Et	Et	Et
Me	Me	Et	Et	Et	Et	Et
Me	Me	Et	Et	Et	Et	Et
Me	Me	Et	Et	Et	Et	Et

TABLE 3. *Infrared frequencies (cm.$^{-1}$) for compounds* (I).

R: Me R′: Me	Me Et	Me Pr^n	Me Pr^i	Me Bu^n	Me n-Pentyl	Me n-Hexyl	Et H	Et Me	Et Et	Et Pr^n	Et Pr^i	Et Bu^n	Et n-Pentyl	Et n-Hexyl	Assignment
							3354m(b)								N–H stretching
2967sh	2965s	2965s	2979s				2976s	2962s	2980s	2954vs	2963s	2942s	2953s		
2936m	2924m	2936s	2937s	2938s	2941vs	2920s	2927s	2929m	2943m	2920s	2927sh	2919s	2927s	2912vs	
			2908m	2918s	2907s										
2872m	2860m	2872s	2878s					2873m	2880m		2874w				
2842m			2844m	2851s	2853s	2845s	2860s	2843m	2863sh	2861s		2851s	2862s	2846s	C–H stretching of CH_3 and CH_2 groups
	2810m	2824s	2821m	2802sh					2826m	2812s	2807w	2816sh			
2776m	2773m	2787s						2785m	2774m				2775m		
	2755m		2756m	2765m	2765m	2769m				2761s		2761m		2766m	
						2735w	2749vw	2736sh			2745w				
2640vw								2704w	2709vw						
2606vw			2613vw		2600vw						2607vw				
1544vs	1543vs	1546vs	1545vs	1541vs	1543vs	1545vs	1540vs	1542vs	1543vs	1543vs	1543vs	1543vs	1542vs	1542vs	NO_2 stretching assym.
1462s	1455m	1458s	1459s	1453s	1453s	1457s	1459s	1462s	1460s	1461s	1460s	1460s	1460s	1460s	CH_2 scissoring
1449s		1442sh					1444sh	1445s	1442s	1440s	1443s	1441s	1443s	1443s	CH_2 scissor. in R = Et
1400m	1402w	1402m	1403m	1399m	1400m	1400m									
	1381m	1381m	1389s				1391m	1390m	1384m	1390s	1386m	1388m		1390m	
			1365s	1376m	1376s	1379m				1378s		1375m	1378m	1373s	
							1357s	1361m	1360m	1359m	1362m	1359m	1359m	1359s	
1354s	1351m	1350s	1352s	1348s	1348s	1349s									NO_2 stretching symm.
			1338m				1341s	1343m	1342m	1342s	1336sh	1341m	1338m	1337s	NO_2 stretching symm.?
	1320sh						1324s	1325s	1325s	1325s	1324m	1326s	1325s	1325s	NO_2 stretch. symm. or CH_2 wagging?
															CH_2 wagging
1302m	1308m	1307s	1307s	1308s	1306s	1308m									
1282m		1277m	1281vw	1277m	1277w	1279w	1282w	1280w		1287m	1281vw	1279w	1288w	1281w	
1260m					1260w			1260s		1273m		1257w	1259w		
1249m			1237s	1246w			1241m	1236w		1244m	1231s		1241w	1237m	
1222m	1219m	1217s	1218s	1213s	1210m	1215m	1203w	1212m	1222s	1211s	1210m	1203s	1207s	1208s	C–N?
				1194m											
1150m			1167m			1176m	1160s	1143m			1164w			1171m	
1128m	1135m	1135s	1127s	1132s	1135s	1132m		1131s	1136s	1127s	1123s	1128s	1128s	1129s	
1113s	1105s	1105s	1109s	1103s	1104s	1107s	1118m	1117s	1108s	1104s		1103s	1106s	1106s	C–O–C in ring
			1096sh			1094s	1099m	1099m			1095sh			1095sh	
1080s	1077s	1079s	1081vs	1080s	1076s	1081s	1064s	1085s	1082s	1080vs	1085s	1086s	1082s		
1053w		1049s	1055m	1045s	1046s	1049m		1057m	1051s	1053s	1057w	1050m	1052s	1053s	
1042m	1046m	1029m	1031m					1045m	1028vw	1030m	1031m	1031w	1028m	1031w	
	1004w	1005m	1005vw	1004w	1004w	1002w	1012s	1025m	1014vw	1015m	1014w	1012vw			
999w	980vw	990m	986w	977w	973vw	982sh		980w	982w	983w	981w				
								964vw	967w	967m	962vw	963w	966vw	966w	
947w	946m	953s	946s	947s	951m	949m	951m	947s	956w	948s	938m	943m	947m	943s	C–O–C in ring
									937m						
912m									911m	912s	909m	910m	914m	914s	
897s	892m	897s	893s	893s	892s	895m	898s	896m	896m			894m	894m		C–N–C and C–N$\langle^{C}_{C}$?
							887sh	881m		884s	885w			889s	
	866vw	869m				869sh									
851m	843m	850s	855m	850s	848s	850m	849s	850s	842m	849s	852w	849m	848m	850s	C–O–C in ring
			820w				816sh	817vw	811vw	817w	817w	815vw	818w	818w	
							796s	788w	788w	789m	788vw	787w	788w	788m	
		776w					764m								
		754w	755vw									735vw			
						725w								724w	

TABLE 4. *Infrared frequencies (cm.$^{-1}$) of compounds* (II).

3347m(b), 2994vs, 2948vs, 2928s, 2893s, 2757w, 2664w, 2613vw, 1459s, 1449s, 1385s, 1369s, 1343m, 1292m, 1260vs, 1212s, 1188s, 1146s, 1115s, 1097s, 1073s, 1043s, 1002vs, 925m, 895m, 818s, 772s, 751s.

TABLE 5. *Infrared frequencies (cm.$^{-1}$) of compounds* (III).

Ar: Ph	*p*-$F{\cdot}C_6H_4$	*o*-$Cl{\cdot}C_6H_4$	*m*-$Cl{\cdot}C_6H_4$	*p*-$Cl{\cdot}C_6H_4$	*p*-$Br{\cdot}C_6H_4$	*o*-$NO_2{\cdot}C_6H_4$	2,3-$(MeO)_2C_6H_3$	Assignment
3052w	3055w	3047w	3048w	3044w	3044w	3061w	3064w	C–H in arom. ring
3020w								
2928m	2930m	2926s	2917s	2921s	2928m	2928m	2920s	C–H stretch. in CH_2 groups
2878m	2878m		2874m	2873m	2872w	2884m	2877sh	
2848m	2850m	2846m	2844m	2843m	2846m	2851m	2835sh	
		2819m						
1649vs	1645vs	1652vs	1645vs	1644vs	1644vs	1659vs	1655vs	C=N conj. with arom. ring
1602w	1599s	1589m	1590m	1591s	1585s	1604m	1592m	
1580m		1562w	1567s			1572m	1575s	
					1520w	1522vs		
1492m				1482s				
1471w	1468m	1465s	1469s	1470sh	1471m	1466m	1469vs	
1448m	1434w	1431s	1422s	1433m	1434w	1434m	1439s	CH_2 scissoring
							1415s	
				1394s	1390m			
1380w	1376w	1377m	1376w					
1349s	1348s	1346vs	1345vs	1345vs	1343s	1349vs	1344vs	CH_2 wagging
							1306s	
	1280s	1290vs	1284s	1280s	1276s	1286s		
1274s	1270s		1255vs	1264vs	1263s	1269s	1261vs	
		1246s				1252s		
1226w	1216s	1221vw	1222m	1222w	1224w	1221w	1231vs	C–N?
1198vw		1195w	1195vw	1198vw	1198vw	1197vw	1181s	
1174w	1150s			1168m	1170m			
1132s	1128vs	1130vs	1131vs	1130vs	1131vs	1127vs	1130s	C–O–C in ring
1105s	1103s	1105vs	1109s	1100vs	1098s	1107s	1119s	
			1090s	1090vs		1086s	1084vs	
1073m		1071s	1074s		1067s			
	1060m	1057s		1058m		1065m	1057s	
1039w	1033vw	1034s	1039m	1030vw	1030vw	1039w	1033s	
1024m	1014m	1023sh		1014s		1024w		
			998w		1008s		1004s	
			941sh				945w	
933m	929w	927m	923m	929w	928w	927m	923w	C–O–C in ring
			896m					
885vw		881vw	882m			878w	885w	C–N=C in ring?
			862s			860m		
856w	844s	852m		843s	835s	847m	836w	
805w	823s	805m	816m	803m	803m	806m	807m	C–O–C in ring
			795s				793m	
783m	786w					783s		
		764s				757m	762m	
	737m	733s	740s	733s	728m		750s	
		719s	711s			721s	708w	
694s								

characterised [8] by exaltation and depression, respectively. Isocyclic six-membered rings do not seem to produce any deviation of the molecular refractivity, but in our instance this may be the influence of two heteroatoms.

Infrared Absorption Spectra.—N–H *stretching vibrations.* The bands 3354 and 3347 cm.$^{-1}$ for the compounds (I; R = Et, R′ = H) and (II) respectively should be assigned to stretching vibrations of the N–H group. The frequency is lowered by intermolecular hydrogen bonds.

Symmetrical C–H *stretching vibrations.* All the substances (I) examined give numerous bands of strong and medium intensity in the region 2980—2700 cm.$^{-1}$ which should be

[8] Asmus, "Refraktometrie," in Houben-Weyl's "Methoden der Organischen Chemie," Thieme Stuttgart, 1955, Vol. III, Part 2.

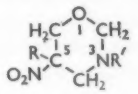
assigned to symmetrical C–H stretching vibrations of methyl and methylene groups. It was difficult to differentiate between various bands by using only a sodium chloride prism; the bands in this region were particularly numerous for compounds of type (I).

Region 1659—1640 *cm.*$^{-1}$. These vibrations are present only for the compounds (III) which differ from (I) and (II) by the absence of O–C–N and the presence of O–C=N bonds. We suggest assigning these frequencies to C=N bonds conjugated with the aromatic ring. The frequencies are similar to C=N vibration frequencies observed by Bergmann *et al.*[9] for aromatic Schiff's bases and by Lynn [5] for derivatives of 2-alkenyl-5,6-dihydro-1,3-oxazines.

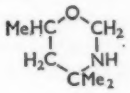
Antisymmetrical NO_2 *stretching vibrations.* Very strong bands at 1546—1540 cm.$^{-1}$ are found in the spectra of compounds (I). Their frequency is shifted towards figures usually assigned to tertiary nitro-paraffins.[10]

Methylene scissoring vibrations. One strong band at 1463—1452 cm.$^{-1}$ is present for all the compounds (I). Another band, at 1445—1440 cm.$^{-1}$, was found in the spectra of the ethyl compounds (I; R = Et) but not in those of the methyl analogues (I; R = Me). This should probably be assigned to CH_2 vibrations of the ethyl group. Two strong bands, at 1459 and 1449 cm.$^{-1}$, are present in the spectrum of the compound (II). The compounds (III) give a band at 1448—1422 cm.$^{-1}$.

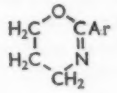
Symmetrical NO_2 *stretching vibrations.* High-intensity bands of frequency 1354—1348 cm.$^{-1}$ are displayed by all the methyl compounds (I; R = Me). They should be assigned to symmetrical NO_2 stretching vibrations. However, the assignment is more complicated for the ethyl compounds (I; R = Et). Two bands near this frequency have



(I)



(II)



(III)

been observed: one of medium intensity at 1342—1336 cm.$^{-1}$, and a strong band at 1326—1324 cm.$^{-1}$. It is difficult to decide which of these two should be assigned to NO_2 vibrations. The former is nearer to the frequency observed with the compounds (I; R = Me) but its intensity is then anomalously low; nevertheless in view of the assignment of methylene wagging vibrations (see below) this frequency should be assigned to NO_2 stretching vibrations.

The difficulty of assigning symmetric nitro-group vibrations has been observed earlier by some of the present authors.[11]

Methylene wagging vibrations. All the compounds (I; R = Me) show a frequency 1308—1302 cm.$^{-1}$ which should be assigned to methylene wagging vibrations, although it is unusually low. Again, with the compounds (I; R = Et) the assignment is more complicated and depends on that of symmetrical NO_2 vibrations. If the frequency 1342—1336 cm.$^{-1}$ is due to the latter vibrations, the frequency 1326—1324 cm.$^{-1}$ should be assigned to methylene wagging vibrations of the ethyl groups.

A medium-strength band at 1343 cm.$^{-1}$ in the spectrum of the compound (II) and strong bands at 1349—1343 cm.$^{-1}$ in the spectra of compounds (III) should also be assigned to methylene wagging vibrations.

Band at 1222—1203 *cm.*$^{-1}$. This is present in the spectra of all the compounds (I) examined, and in (II). For compounds (III) the frequency of this band is slightly higher (1231—1216 cm.$^{-1}$). It is probable that it corresponds to C–N vibrations, which are not sufficiently well described in the literature.[12]

[9] Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 168.
[10] Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 6341.
[11] Eckstein, Fluksik, and Sobótka, *Bull. Acad. Polon. Sci., Sér. Sci. chim. géol. géograph.*, 1959, **7**, 803.
[12] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.

XUM

1,3-*Oxazine ring vibrations.* According to the literature [5] the bands of the 1,3-oxazine ring lie in the region of 1150—1050 cm.$^{-1}$. In the spectra of the compounds (I) three strong bands with frequencies 1136—1117, 1113—1099 and 1086—1076 cm.$^{-1}$ were observed. The compound (II) gives strong bands at 1146, 1115, 1097, and 1073 cm.$^{-1}$, and the compounds (III) give bands at 1132—1127, 1119—1098, and 1086—1067 cm.$^{-1}$. In some instances the band is doubled (*e.g.*, for III where Ar = *m*-Cl·C_6H_4). The frequencies agree with the view expressed by Bergmann and his collaborators [5,9,13] who assigned these frequencies to vibrations of the system N–C–O in oxazolidines. Bergmann and Pinchas [14] had earlier found five bands for the bonds C–O–C in acetals and ketals; three of them (1143—1124, 1116—1105, and 1098—1063 cm.$^{-1}$) are found in our spectra. Lagrange and Mastagli,[15] and Barker, Bourne, Pinkard, and Whiffen,[16] are in agreement with Bergmann and Pinchas.

Also some lower-frequency bands of medium intensity, namely 953—937 and 855—842 cm.$^{-1}$ for compounds (I), 925 and 818 cm.$^{-1}$ for (II), 933—927 and 823—803 cm.$^{-1}$ (of variable intensity) for compounds (III), are probably due to cyclic acetal vibrations, in agreement with Barker *et al.*[16]

***Band near* 890 *cm.*$^{-1}$.** In the spectra of the compounds (I) bands of frequency 898—884 cm.$^{-1}$ are present. They correspond to the frequency 895 cm.$^{-1}$ for (II). It is difficult to assign them to any known vibration and we suggest vibrations C–N–C and C–N$\begin{smallmatrix}\diagup\mathrm{C}\\ \diagdown\mathrm{C}\end{smallmatrix}$ in the 1,3-oxazine ring. The frequency is lower for the compounds (III), 885—835 cm.$^{-1}$, owing to a different structure (C=N–C).

The absence of bands corresponding to O–H stretching vibrations in the spectra of the compounds (I) which were prepared from nitro-diols, formaldehyde, and ammonia or amines seems to be final evidence of their cyclic structure. At the same time a new proof has been found that the C–O–C fragment of the 1,3-oxazine ring is of acetal character.

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WARSAW 10, POLAND. [*Received, April 4th,* 1960.]

[13] Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 237.
[14] Bergmann and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 161.
[15] Lagrange and Mastagli, *Compt. rend.*, 1955, **241**, 1947.
[16] Barker, Bourne, Pinkard, and Whiffen, *J.*, 1959, 802, 807.

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98. *Molecular Complexes exhibiting Polarization Bonding. Part III.*[1] *A Structural Survey of Some Aromatic Complexes.*

By S. C. WALLWORK.

The molecular orientations and intermolecular separations in the crystal structures of a number of aromatic complexes are discussed. It is concluded that polarization bonding in such complexes results in a characteristic plane-to-plane packing of the components and that, where charge-transfer forces might be significant in determining the structure, the relative dispositions of the components are such as to allow the maximum degree of overlap between their molecular π-orbitals.

THE term "polarization bonding" was first used by McKeown, Ubbelohde, and Woodward [2] to describe what was thought to be a close intermolecular approach in a structure suggested [3] for *p*-nitroaniline. Although it is now known that this structure is incorrect [4] and that there is no such close approach in the correct structure, it is convenient

[1] Part II, Harding and Wallwork, *Acta Cryst.*, 1955, **8**, 787.
[2] McKeown, Ubbelohde, and Woodward, *Acta Cryst.*, 1951, **4**, 391.
[3] Abrahams and Robertson, *Acta Cryst.*, 1948, **1**, 252.
[4] Donohue and Trueblood, *Acta Cryst.*, 1956, **9**, 960.

XUM

to retain the term " polarization bonding " to describe the intermolecular attraction found in certain molecular complexes. The class of molecular complexes is exemplified by the complexes formed by *s*-trinitrobenzene with aromatic hydrocarbons, by the quinhydrones, and by the iodine–aromatic hydrocarbon complexes. " Polarization bonding " is intended to include both charge-transfer bonding described by Mulliken [5] and the weaker interaction, between polar groups on one component and a polarizable second component, described by Briegleb.[6] It therefore leaves open the question of the precise nature of the interaction in any particular case.

Preliminary structural data are now presented for a number of polarization-bonded complexes. The crystal structures of the phenol–*p*-benzoquinone [7] and the chloranil–hexamethylbenzene [1] complexes have already been reported in some detail * and full accounts of the crystal structures of most of the other complexes mentioned will be presented later. Most of these structures are awaiting further refinement on the basis of better *X*-ray data from low-temperature photographs. Meanwhile a preliminary report may be of value since some reliable information can be given about the arrangement of the molecules in the crystal lattices.

Before discussing the experimental data, the structural effects to be expected from polarization bonding will be considered. For weak bonding, arising from the interaction of polarizing groups and polarizable molecules, the main feature to be expected is the juxtaposition of the polarizing groups of one component and the most polarizable regions of the other component. To be certain that such a juxtaposition does not arise merely because this represents the most efficient way of packing together particular shapes of molecules, it would be necessary to observe similar tendencies in related complexes containing molecules of shapes varying as widely as possible. Besides causing particular orientations of molecules, such weak polarization bonding might be expected to result in a slight decrease in the van der Waals separation of the mutually attracting molecular regions.

For charge-transfer complexes the question of the relative orientation of the two components has been discussed by Mulliken.[5] The stabilization of the complex depends upon overlap between the highest filled molecular orbital of the donor molecule and the lowest unfilled molecular orbital of the acceptor molecule. The extent of this overlap depends upon the symmetries of these two orbitals and the relative orientations of the molecules. For complexes where both the donor and the acceptor molecules are aromatic Mulliken's theory predicts that they will be superimposed plane to plane and, in the case of mononuclear aromatic molecules, probably will lie in the same orientation with the centres of the rings directly over each other. Packing considerations and polarizations of the type considered above might distort this arrangement in some cases, however. Again, an intermolecular separation less than normal is to be expected, the decrease being greater for larger charge-transfer stabilization of the ground state of the complex.

Small reductions in van der Waals separations are very difficult to establish. In the first place a " normal " van der Waals separation is probably better represented by a range than by a definite value. This is because it represents the balance between repulsive forces and weak attractive forces which depend upon the particular crystal structure. Secondly, the range of values to be accepted as " normal " is not well established. Thirdly, from a consideration of the shapes of the electron charge-clouds, one should probably not expect the van der Waals radii to be the same for plane-to-plane molecular packing as for the edge-to-plane packing which is common in the crystal structures of small aromatic molecules. Fourthly, although the van der Waals separation should strictly be measured

* The unusual standard deviations [1] to which attention has been drawn [4] are incorrect. The recalculated values (in Å) are: for carbon $\sigma_x = 0{\cdot}085$, $\sigma_y = \sigma_z = 0{\cdot}023$; for oxygen $\sigma_x = 0{\cdot}044$, $\sigma_y = \sigma_z = 0{\cdot}016$; for chlorine $\sigma_x = 0{\cdot}022$, $\sigma_y = \sigma_z = 0{\cdot}008$. These values suggest that the reported distortions of the molecules are probably not significant.

[5] Mulliken, *J. Amer. Chem. Soc.*, 1950, **72**, 600; 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801.
[6] Briegleb, " Zwischenmolekulare Kräfte und Molekülstruktur," Enke, Stuttgart, 1937.
[7] Wallwork and Harding, *Acta Cryst.*, 1953, **6**, 791.

XUM

between atomic centres, the perpendicular separation between molecular planes, irrespective of the precise positions of the atoms, is a quantity much more conveniently measured and discussed in structures with plane-to-plane packing. The best guide that one has for structures of the latter type is that both in graphite and in crystals of large polynuclear aromatic molecules [8] the perpendicular distance between the layers is about 3·4 Å.

Experimental Results

A common feature in all the structures now described is a plane-to-plane stacking of the components. In every case but one the stoicheiometric ratio of the components in the complexes is 1 : 1, and the two types of molecule are arranged alternately in an infinite stack. The exception is the complex between phenol and benzoquinone where the ratio of 2 : 1 seems to be determined by hydrogen-bonding requirements,[7] and the molecules are arranged in groups of three with each quinone molecule sandwiched between two phenol molecules. This plane-to-plane arrangement is consistent with the inference that each of the complexes described is of the charge-transfer type. It is not essential that this inference should be made in every case, however, since a plane-to-plane arrangement is the typical mode of crystallization of large polynuclear aromatic molecules [8] and even of hexamethylbenzene.[9] The problem may be considered further, however, in the light of the relative positions of the component molecules and their intermolecular separations. Although the positions of the atoms are known with varying degrees of accuracy in the structures described in this paper, there is no doubt about the overall positions of the molecules, and their orientations are known fairly accurately in many cases. If the axis along which the molecules are stacked is known, division of the length of the repeat unit of this axis by the number of molecules in the unit gives the average separation

Donor	Ionisation potential (ev)	Separation along stack (Å)	Perpendicular separation (Å)
Acceptor: s-*trinitrobenzene*			
Benzene	9·245 [10]	3·68	?
Naphthalene	8·12 [10]	3·49	3·45
Anthracene	7·4 [11]	3·31	3·28
Benzidine	—	3·54	(3·32)
Acceptor: *benzoquinone* (*Redox potential* 0·71 v)			
Phenol	8·50 [10]	3·87	3·33
Quinol	—	3·84	3·16 [12]
Acceptor: *chloranil* (*Redox potential* 0·742 v)			
Hexamethylbenzene	8·0 [11]	3·65	3·51
Dimethylaniline	7·3 [11]	3·40	(3·40)
Tetramethyl-*p*-phenylenediamine	6·6 [11]	3·26	3·26
Acceptor: *bromanil* (*Redox potential* 0·746 v)			
Tetramethyl-*p*-phenylenediamine	6·6 [11]	3·31	3·31

of molecules along the stack. If also the orientation of the molecules relative to this stacking axis is known with reasonable certainty the average perpendicular separation between molecules can be calculated. In the Table both these values are quoted for the molecular compounds investigated. Where the orientation of molecules is uncertain the value for the perpendicular separation is given in parentheses. For convenience, the compounds have been classified in terms of donor and acceptor molecules irrespective of whether or not the charge-transfer character which this classification implies is justified. The acceptors for all groups except the first are *p*-benzoquinones. According to Mulliken's theory of charge-transfer complexes,[5] the stabilisation energies of a series of complexes formed by the same acceptor would be expected to increase with decreasing ionization potentials of the respective donors. If the acceptor molecules in the series are similar in type and contain atoms of similar van der Waals radii it is

[8] Robertson and White, *J.*, 1945, 607; White, *ibid.*, 1948, 1398; Donaldson and Robertson, *Proc. Roy. Soc.*, 1953, *A*, **220**, 157; Donaldson, Robertson, and White, *ibid.*, 1953, *A*, **220**, 311.
[9] Brockway and Robertson, *J.*, 1939, 1324.
[10] Watanabe, *J. Chem. Phys.*, 1957, **26**, 542.
[11] Briegleb and Czekalla, *Z. Elektrochem.*, 1959, **63**, 6.
[12] Matsuda, Osaki, and Nitta, *Bull. Chem. Soc. Japan*, 1958, **31**, 611.

to be expected that the complexes with higher stabilization energy will have smaller average perpendicular separations between the molecules. In the Table the ionization potentials of the donors are given where these are available, and it may be seen that in each of the series for which the relevant information is available the perpendicular separations follow the expected trend.

The above limitations being borne in mind, it would seem that the average perpendicular separations of the components in nearly all the complexes shown in the Table are less than the expected van der Waals separations. This is particularly true of the complexes of *NNN'N'*-tetramethyl-*p*-phenylenediamine with chloranil and bromanil where the separations are **3·26** and **3·31** Å, respectively. It is interesting that these are among the complexes for which paramagnetism has been reported.[13] The paramagnetism was sought for in these complexes because it was considered that they might be largely ionic in the ground state (*i.e.*, consisting of molecular ions D^+A^-, where D and A represent donor and acceptor respectively); a largely ionic structure should result in molecular separations smaller than those observed. (It might be argued that the close approaches need not be along the stack of molecules but could occur in

FIG. 1. *The relative orientations of the molecules in the complexes of* s-*trinitrobenzene with naphthalene and benzidine.*

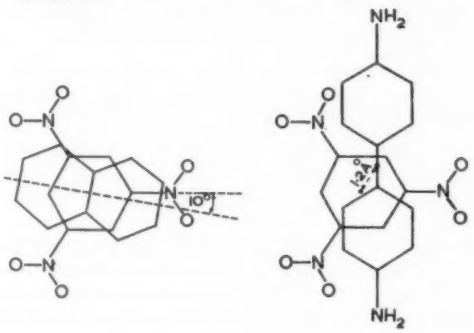
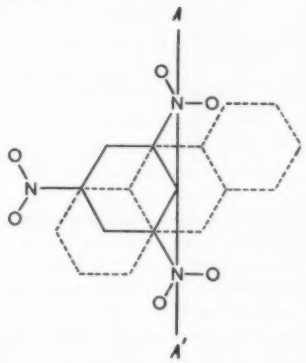


FIG. 2. *Two of the four molecules in a repeat unit of a column of the* s-*trinitrobenzene and anthracene complex. The two further molecules which are superimposed on them are seen in projection by reflecting the first two about the line AA'.*



a sideways direction if the charge were appropriately localized. However, all the sideways contacts appear to be normal van der Waals separations.)

The other structural feature of interest is the relative orientations of the component molecules. In the trinitrobenzene series this has not been determined for the benzene complex, but the results for the complexes with naphthalene, benzidine, and anthracene are illustrated in Figs. 1 and 2. It can be seen that the aromatic rings of the two components have similar orientations in the anthracene complex but not in the naphthalene and benzidine complexes. This might imply charge-transfer interaction in the anthracene complex and, in fact, a model having an anthracene–trinitrobenzene pair with the same relative orientations and with central nuclei exactly superimposed has recently been suggested [14] on the grounds of symmetry necessary for charge-transfer interaction, and has been used to interpret successfully the absorption and luminescence spectra of this complex. However, in the crystalline complex the central nuclei in adjacent molecules are shifted sideways through approximately **1·4** Å from the position where they would be directly under each other. The interpretation of this shift is not possible until more detailed information is available about this and similar structures. However, this effect in the anthracene complex and the lack of parallel orientation in the naphthalene

[13] Kainer, Bijl, and Rose-Innes, *Naturwiss.*, 1954, **41**, 303; Kainer and Überle, *Chem. Ber.*, 1955, **8**, 1147; Bijl, Kainer, and Rose-Innes, *J. Chem. Phys.*, 1959, **30**, 765.
[14] McGlynn and Boggus, *J. Amer. Chem. Soc.*, 1958, **80**, 5096.

XUM

and benzidine complexes suggest that if there are charge transfer forces operating in the crystal lattices of any of these trinitrobenzene complexes they must be weak. This conclusion may seem rather surprising in view of the calculations by Briegleb and Czeckalla [15] based on the spectra of trinitrobenzene complexes in solution. These authors deduce that charge transfer accounts for about half the energy of stabilisation of the ground state of such complexes. However, in the crystalline state, other lattice forces may be more important and may have the determining influence on the molecular orientation.

The two members of the quinhydrone series show similar orientations of the two components, but again the centres of the aromatic nuclei are not directly over each other. The relative orientations and shifts found for phenoquinone are shown in Fig. 3. By comparison of cell dimensions a similar structural arrangement for quinhydrone was postulated [16] and has more recently been confirmed.[12] From the detailed structure determination the shift of the centre of each quinol molecule relative to that of the adjacent quinone molecule is known to be about 2·1 Å in the direction of the C=O group. In these two structures the shifts can be attributed

FIG. 3. *A group of two phenol molecules and one quinone molecule in phenoquinone, showing the sideways shifts of the molecular centres.*

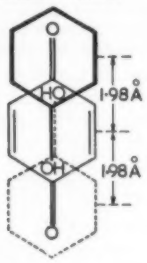
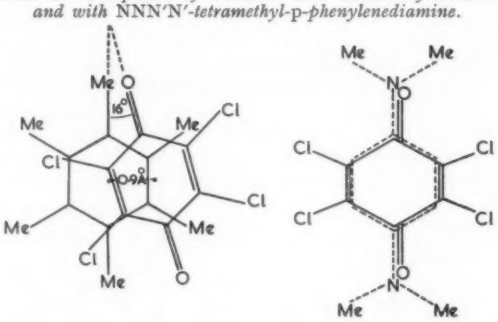


FIG. 4. *Complexes of choranil with hexamethylbenzene and with* NNN'N'*-tetramethyl-*p*-phenylenediamine.*



to the compromise with hydrogen-bonding requirements, and the parallel orientations and short perpendicular separation can be taken as being indicative of charge-transfer stabilisation by overlap of molecular π-orbitals. This indication is supported by the remarkable pleochroism of quinhydrones [17] with the maximum absorption of light when its electric vector is parallel to a molecular stack.

The chloranil complexes give more definite indications of the orientating effect of the forces acting between the molecules in each stack. In the complex with hexamethylbenzene the rather large substituents cause the aromatic nuclei of adjacent molecules to differ in orientation by about 16°, and their centres are also shifted through about 0·9 Å relative to each other (see Fig. 4). No detailed information is yet available for the complex with dimethylaniline, but that formed with the more basic *NNN'N'*-tetramethyl-*p*-phenylenediamine is the most interesting. In this case the two component molecules lie directly over one another in the stack and have the same orientation (within the limits of experimental error). It is probably significant that this most suitable orientation for overlap of molecular π-orbitals is associated with one of the shortest perpendicular separations in the Table. There seems to be no doubt that charge-transfer by overlap of π-orbitals is the determining feature of this structure. The complex formed by the same base with bromanil as acceptor is very similar to that just described. There is again the direct superposition of components in the stack but they are separated by 3·31 Å in this case. The increase over the corresponding value for the chloranil complex can be attributed to the larger bromine atoms, and there is other evidence [13] that the charge-transfer forces are larger for the bromanil than for the chloranil complex.

The general conclusions that can be drawn from this work are: (*a*) polarization bonding in complexes between aromatic molecules results in a characteristic plane-to-plane structure in the crystal lattice; (*b*) where charge transfer forces might be expected to be more significant

[15] Briegleb and Czeckalla, *Z. Elektrochem.*, 1955, **59**, 184.
[16] Wallwork and Harding, *Nature*, 1953, **171**, 40.
[17] Nakamoto, *J. Amer. Chem. Soc.*, 1952, **74**, 1739.

in determining the structure (*e.g.*, from low ionization potential of the donor) the relative orientation and positions of the components are found to be such as to allow the maximum degree of overlap between their molecular π-orbitals. These conclusions are in agreement with the views expressed by Briegleb [6] and Mulliken [5] on the interactions in such molecules.

Drs. T. T. Harding, A. Wilson, and D. J. Daniels collaborated with the author in determining the crystal structures discussed in this paper. Thanks are due to the Council of the Royal Society for a contribution to the cost of the apparatus.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 11th*, 1960.]

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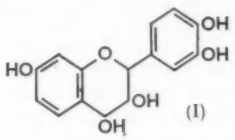
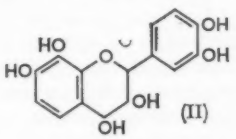
99. *Flavan Derivatives. Part IV.*[1] *Teracacidin, a New Leucoanthocyanidin from* Acacia intertexta.

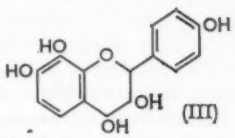
By J. W. CLARK-LEWIS, G. F. KATEKAR, and P. I. MORTIMER.

Heartwood of *Acacia intertexta* contains a new leucoanthocyanidin (teracacidin) found to be (−)-7,8,4′-trihydroxy-2,3-*cis*-flavan-3,4-*cis*-diol, an analogue of melacacidin. The wood also contains a very small proportion of isoteracacidin, and (+)-pinitol. Teracacidin and isoteracacidin appear to be related to each other in the same way as melacacidin and isomelacacidin,[1] and the epimers thus differ only in configuration at the 4-position.

ACACIA is a large genus of the Leguminosæ family and some two-thirds of its five [2] or eight [3] hundred species are indigenous to Australia, although apparently none is a native of New Zealand or Europe.[2] The Australian species *A. mollissima* (black wattle) is extensively cultivated in South Africa as an important source of industrial tanning material, and this species contains the leucoanthocyanidin mollisacacidin (I) isolated by Keppler [4] soon after the discovery in *A. melanoxylon* (Australian blackwood) of melacacidin (II),[5] which also occurs in *A. harpophylla* and *A. excelsa*.[1] A third member, teracacidin (III), of the *Acacia* leucoanthocyanidin series has now been isolated from *A. intertexta*,


(I)


(II)


(III)

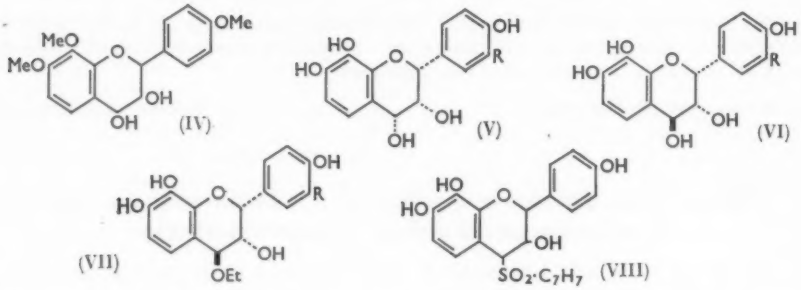
where it occurs with an isomer (isoteracacidin) which is considered to be the 4-epimer, and thus related to teracacidin in the same way as isomelacacidin [1] is related to melacacidin. It is noteworthy also that teracacidin is the first natural representative of flavonoids with the 7,8,4′-pattern of phenolic hydroxylation.

The structure of teracacidin (III) was established by oxidation of its non-phenolic trimethyl ether (IV) to 2-hydroxy-3,4-dimethoxybenzoic acid and *p*-methoxybenzoic acid, which were isolated and characterised as their methyl esters. The course of this oxidation thus corresponds to the similar reaction with melacacidin tetramethyl ether, and the leucoanthocyanidin properties of teracacidin support the flavan-3,4-diol formulation. The teracacidin structure (III) was confirmed by synthesis of the 2,3-*cis*-3,4-*cis*-racemate of 7,8,4′-trimethoxyflavan-3,4-diol (IV) by catalytic hydrogenation of 7,8,4′-trimethoxyflavonol, which gave a product with infrared absorption indistinguishable from that of the lævorotatory teracacidin trimethyl ether, but markedly different from the absorption

[1] Part III, Clark-Lewis and Mortimer, *J.*, 1960, 4106.
[2] Black, " Flora of South Australia," 2nd edn., Government Printer, Adelaide, 1948—1957.
[3] Ewart, " Flora of Victoria," Government Printer, Melbourne, 1930.
[4] Keppler, *J.*, 1957, 2721.
[5] King and Bottomley, *J.*, 1954, 1399.

XUM

of the 2,3-*trans*-3,4-*cis*-racemate prepared from *trans*-dihydro-7,8,4′-trimethoxyflavonol by reduction with sodium borohydride or by hydrogenation over palladium. Teracacidin (V; R = H) is thus stereochemically identical with melacacidin (V; R = OH).



The chemical and chromatographic behaviour of melacacidin (V; R = OH), isomelacacidin (VI; R = OH), and *O*-ethylisomelacacidin [1] (VII; R = OH) closely resembles the behaviour of compounds in the teracacidin series, and this indicates a similar relation between teracacidin (V; R = H), isoteracacidin (VI; R = H), and *O*-ethylisoteracacidin (VII; R = H). Thus a small proportion of isoteracacidin occurred with teracacidin, and when warmed with ethanolic acetic acid it was converted into *O*-ethylisoteracacidin (VII; R = H); this derivative was readily hydrolysed to isoteracacidin again, just as *O*-ethylisomelacacidin was readily hydrolysed to isomelacacidin. Unlike the melacacidin series, however, the teracacidin compounds have remained amorphous even when chromatographically homogeneous, and formulation of isoteracacidin as the 4-epimer (VI; R = H) and *O*-ethylisoteracacidin (VII; R = H) as its 4-ethyl ether rests largely on analogy with the melacacidin compounds. The isoteracacidin fraction, obtained by counter-current distribution of the *O*-ethyl derivative and subsequent hydrolysis, was converted by reaction with toluene-*p*-sulphinic acid into the sulphone [1] (VIII), the only crystalline phenolic compound so far obtained in the teracacidin series. This sulphone yielded also a crystalline tetra-acetate, and was converted by hot acid into the same anthocyanidin as was obtained from teracacidin, and in all these reactions isoteracacidin resembles isomelacacidin. Investigation of the teracacidin compounds was made more difficult by their occurring in the heartwood with comparatively large quantities of extractable brown polymers (" phlobaphenes ").

The stereochemical representations in the formulæ (V—VII) are supported by the similarity in molecular rotations of the methyl ethers, the sulphones, and the acetylated sulphones in the teracacidin series (−214°, −110°, −86°) with those of the melacacidin compounds (−309°, −118°, −88°), and by synthesis of the racemic trimethyl ether (IV) corresponding to (V; R = H). This synthesis was achieved by catalytic hydrogenation of 7,8,4′-trimethoxyflavonol by the method introduced for synthesising (±)-melacacidin tetramethyl ether,[6] which is the only route so far available for preparing all-*cis*-flavan-3,4-diols. Teracacidin trimethyl ether was thus obtained, but with more difficulty than for melacacidin tetramethyl ether which appears to be a very favourable case. Raney nickel catalysts with low activity leave the flavonols unaffected, and fresh W7 and W6 catalysts usually carry the hydrogenation too far through hydrogenolysis of the 4-hydroxyl group and, mainly, further hydrogenolysis to phenolic 1,3-diarylpropan-2-ols. Best yields of flavan-3,4-diols so far have attended the use of W6 catalyst stored at 0° under ethanol for 4—6 months before use.

Pinitol occurs widely in the Leguminosæ [7] and has been isolated from wood of *A.*

[6] King and Clark-Lewis, *J.*, 1955, 3384.
[7] Plouvier, *Compt. rend.*, 1955, **241**, 1838.

mollissima.[4,8] Pinitol sometimes crystallised from our acetone extracts of *A. melanoxylon* (*ca.* 0·9%) and *A. mollissima* (1·5%) heartwoods; it was also isolated from *A. intertexta* (0·3%) and *A. harpophylla* (0·05%) heartwoods, and was detected in *A. excelsa*. Demethylation of (+)-pinitol to (+)-inositol was found to occur readily in boiling 6N-hydrochloric acid, which may therefore be used for this purpose instead of hydriodic acid.[9]

Experimental

Paper chromatograms of anthocyanidins were run with Forestal solvent [10] and butanol–acetic acid–water [11] (4 : 1 : 5) was used for other phenols and for cyclitols, except where otherwise stated.

Wood specimens were collected by Mr. W. T. Jones, C.S.I.R.O., Brisbane, from botanically identified *Acacia intertexta* (herbarium number 473) and supplied by courtesy of the Chemical Research Laboratories, C.S.I.R.O., Melbourne.

Extraction of Pinitol and Leucoanthocyanidins from A. intertexta *Heartwood*.—The milled wood (3130 g.) was extracted by continuous hot percolation with light petroleum (b. p. 60—80°) for 12 hr. (4·5 g. of extractive), acetone (24 hr.), and ethanol (8 hr.); the acetone and ethanol extractives contained pinitol, teracacidin, and isoteracacidin. Evaporation of the acetone extract left a viscous residue (312 g.) which was stirred with water (2 l.) and filtered next day from a considerable quantity of amorphous deposit. The filtrate was concentrated (to 250 c.c.) under reduced pressure, and continuous extraction with ethyl acetate then yielded 22 g., 2·1 g., and 0·7 g. of polyphenolic material in successive 8 hr. periods, and left pinitol (*ca.* 17 g.) in the aqueous phase. The ethanol extract was similarly treated and gave 6·9 g. of material soluble in ethyl acetate; 4·3 g. remained in the aqueous phase. Crystallisation, from aqueous ethanol, of the pinitol fractions (from 11·5 kg. of heartwood) gave pinitol (40 g., 0·35%), m. p. 182—183° after recrystallisation from aqueous ethanol, $[\alpha]_D^{16}$ +65° (2·8% in H_2O) (Found: C, 43·0; H, 7·3; OMe, 15·6. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; OMe, 16·0%). When chromatographed for 45 hr. pinitol moved 15 cm. and two unidentified polyol components moved 8·5 and 1·9 cm.

The combined ethyl acetate-soluble polyphenols (32 g.) were submitted to a 50-tube (50 c.c.) counter-current distribution between ethyl acetate and 0·067M-phosphate buffer (pH 7·0). Tubes 24—36 (peak at 29) contained teracacidin (R_F 0·46—0·54) and isoteracacidin (R_F 0·58—0·68), and the contents were collected; the ethyl acetate phases were combined with ethyl acetate extracts of the aqueous phases and dried (Na_2SO_4). Evaporation left a residue (4·8 g.) containing mainly teracacidin (R_F 0·46—0·54) and some *O*-ethylisoteracacidin (R_F 0·75—0·87) (an artefact formed during manipulation of the extracts with ethanol). A 2% aqueous solution of this residue was heated at 100° for 2 hr. and the solution then contained teracacidin (R_F 0·47—0·54) and a little isoteracacidin (R_F 0·58—0·64) but no *O*-ethylisoteracacidin (R_F 0·78—0·85); R_F values for teracacidin, isoteracacidin, and *O*-ethylisoteracacidin in 2% acetic acid were 0·41—0·52, 0·58—0·68, and 0·67—0·76. In this way, *A. intertexta* heartwood (9·1 kg.) gave a teracacidin fraction (16·8 g., tubes 24—36) and further polyphenols (80 g., tubes 37—50). The teracacidin fraction (16·8 g.) was boiled in 1% ethanolic acetic acid (170 c.c.) for 2 hr. and evaporated before counter-current distribution once more; tubes 24—40 (peak at 32) contained only teracacidin (5·1 g., 0·06%). Another sample of wood (580 g.) gave a much higher yield of teracacidin (0·5%).

Isoteracacidin Sulphone (VIII) *and its Tetra-acetate*.—Polyphenols (92 g.) from tubes 37—50 of the above counter-current distributions were heated for 2 hr. at 100° with water (600 c.c.) and acetic acid (12 c.c.), and soluble material was isolated (less than 20 g.) and converted into *O*-ethylisoteracacidin with boiling 1% ethanolic acetic acid. Evaporation left a residue which failed to crystallise and was accordingly dissolved in ethanol (23 c.c.), diluted with water (100 c.c.), and filtered from amorphous material. The filtrate was boiled for 10 min. with concentrated hydrochloric acid (0·1 c.c.), then sodium toluene-*p*-sulphinate dihydrate (10 g.) in water (20 c.c.) and acetic acid (6 c.c.) was added, and the mixture was heated on a steam-bath for 30 min. Crystallisation gave the crude sulphone (3·4 g.) and recrystallisation from

[8] Stephen, *J. Sci. Food Agric.*, 1952, **3**, 37.
[9] Stephen, *J.*, 1952, 738; cf. Maquenne, *Compt. rend.*, 1889, **109**, 813.
[10] Bate-Smith, *Biochem. J.*, 1954, **58**, 122.
[11] Partridge, *Biochem. J.*, 1948, **42**, 238.

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5% acetic acid (charcoal) gave *isoteracacidin* p-*tolyl sulphone* (2·16 g.) which crystallised from aqueous acetone (44 c.c.; 1 : 1) in clusters of transparent plates which became opaque when dried in air (1·3 g.) and had m. p. 214° (decomp.), $[\alpha]_D^{24}$ −22·4° (1% in acetone) (Found: C, 60·6; H, 5·1; S, 7·3. $C_{22}H_{20}O_7S,\frac{1}{2}H_2O$ requires C, 60·4; H, 4·8; S, 7·3%). Acetylation of the sulphone (0·1 g.) with acetic anhydride (0·4 c.c.) and pyridine (2 c.c.) at room temperature during 14 hr. gave *isoteracacidin* p-*tolyl sulphone tetra-acetate*, which crystallised from methanol (2—3 c.c.) in needles (0·085 g.), m. p. 133—136° raised by recrystallisation from ethanol (67% recovery) to m. p. 137—138°, $[\alpha]_D^{24}$ −16° (1% in acetone) (Found: C, 60·3; H, 5·0; S, 5·4; Ac, 27·4. $C_{30}H_{28}O_{11}S$ requires C, 60·4; H, 4·7; S, 5·4; Ac, 28·8%).

Teracacidin (III) *and Teracacidin* 7,8,4′-*Trimethyl Ether* (IV).—Teracacidin, purified by counter-current distribution as already described, was obtained as a brown powder which gave a red colour when heated in 3N-hydrochloric acid at 100° for 15 min. The solution was extracted with pentyl alcohol, and the orange-red anthocyanidin (R_F 0·74) was compared chromatographically in Forestal solvent (6 hr.; solvent front moved 20 cm.) with cyanidin (R_F 0·55) and 3,7,8,3′,4′-pentahydroxyflavylium chloride (R_F 0·58). The anthocyanidin (R_F 0·74) similarly derived from isoteracacidin sulphone was indistinguishable from that from teracacidin.

Crude teracacidin (1·63 g.) was methylated for 5 hr. in acetone with methyl sulphate (3 g.) and potassium carbonate (10 g.); crystallisation of the product from ethanol gave *teracacidin* 7,8,4′-*trimethyl ether* in small needles (0·5 g.), m. p. 159°, $[\alpha]_D^{18}$ −65% (1% in ethanol) (Found: C, 64·9; H, 6·0; OMe, 28·0. $C_{18}H_{20}O_6$ requires C, 65·0; H, 6·1; OMe, 28·0%). The trimethyl ether was also obtained by methylating the leucoanthocyanidin with diazomethane. (−)-Teracacidin trimethyl ether gave an *isopropylidene derivative* which crystallised from methanol in needles, m. p. 139—140° (Found: C, 67·8; H, 6·5. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%).

Oxidation of Teracacidin Trimethyl Ether (IV).—(*a*) Powdered potassium permanganate (0·51 g.) was added gradually to teracacidin trimethyl ether (0·108 g.) in dry acetone (50 c.c.), heated on a water-bath, until the permanganate colour persisted. The deposit was collected, suspended in 5% sulphuric acid (20 c.c.), decolorised with sulphur dioxide, and heated to the b. p. before filtration. Crystallisation, and purification of the product by dissolution in aqueous sodium hydrogen carbonate (charcoal) and re-acidification, gave *p*-anisic acid (0·0166 g.), m. p. 160—177° raised to m. p. 178° (0·0121 g., 24%) by sublimation at 150° under reduced pressure. A mixture of the product with *p*-anisic acid (m. p. 180—181°) melted at 180—181°, and a mixture with veratric acid (m. p. 180°) melted at 142—145°.

(*b*) Teracacidin trimethyl ether (1·03 g.) was boiled in acetone (50 c.c.) for 4 hr. with potassium permanganate (1·5 g.). Acetone was then evaporated while water (50 c.c.) was added simultaneously. 10% Sulphuric acid (5 c.c.) was then added and manganese dioxide was dissolved with sulphur dioxide. The aqueous suspension of organic substances was extracted with ether (100 c.c. and 4 × 50 c.c.), and the combined ethereal solutions were washed with water (2 × 5 c.c.) before being extracted with 5% aqueous sodium carbonate (5 × 10 c.c.). Evaporation of the ether left a residue (0·14 g.) which gave teracacidin trimethyl ether (0·081 g.) in needles (from benzene), m. p. and mixed m. p. 159°. The sodium carbonate solution was acidified with sulphuric acid and extracted with ether (20 c.c. and 3 × 10 c.c.). Evaporation of the ether left a residue (0·67 g.) which was methylated with ethereal diazomethane (from 4 g. of nitrosomethylurea) for 5 min. The mixture was then separated with aqueous sodium hydroxide into non-phenolic and phenolic products, which gave methyl *p*-anisate (0·34 g., 76%), plates [from light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 48—49°, and methyl 2-hydroxy-3,4-dimethoxybenzoate (0·29 g.) which crystallised from aqueous methanol in prisms (0·25 g., 48%), m. p. and mixed m. p. 75—76°.

(±)-7,8,4′-*Trimethoxy*-2,3-cis-*flavan*-3,4-cis-*diol* (IV).—2-Hydroxy-3,4,4′-trimethoxychalcone [12] (5 g.) was converted into 7,8,4′-trimethoxyflavonol with alkaline peroxide as described for the tetramethoxy-analogue.[5] The flavonol (3·5 g., 70%) crystallised from acetic acid in yellow needles, m. p. 195° (Kostanecki and Schreiber [12] record m. p. 198° for the compound prepared from the hydroxyiminoflavanone) (Found: C, 66·4; H, 5·0. Calc. for $C_{18}H_{16}O_6$: C, 65·9; H, 4·9%). 7,8,4′-Trimethoxyflavonol (2·0 g.) in ethanol (100 c.c.) was hydrogenated for 24 hr. at 100°/100 atm. over aged Raney nickel (W6) (*ca.* 2 g.). The suspension was filtered (kieselguhr) from the catalyst and evaporation of the filtrate under reduced pressure left a residue (1·0 g.) which was chromatographed on alumina (100 g.) deactivated with water (10 g.).

[12] Kostanecki and Schreiber, *Ber.*, 1905, **38**, 2748.

XUM

The column was developed with benzene (150 c.c.), with benzene–ether (1 : 1) (350 c.c.) which yielded an oil (0·39 g.), and then with benzene–ether (1 : 1) (150 c.c.) containing 1% of ethanol which gave the diol (0·36 g., 18%), m. p. 130—132°. (±)-7,8,4′-*Trimethoxy*-2,3-cis-*flavan*-3,4-cis-*diol* crystallised from ethanol in needles, m. p. 132—133° (Found: C, 65·1; H, 6·2. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%). Acetylation of the diol with acetic anhydride–pyridine at room temperature gave the *diacetate* which crystallised from ethanol in leaflets, m. p. 158—159° (Found: C, 63·3; H, 5·7. $C_{22}H_{24}O_8$ requires C, 63·5; H, 5·8%). The *isopropylidene derivative* (prepared as for the melacacidin analogue [6]) crystallised from methanol in needles, m. p. 126° (Found: C, 67·7; H, 6·5. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%).

(±)-2,3-trans-*Dihydro*-7,8,4′-*trimethoxyflavonol*.—Bromine (0·25 g.) in carbon tetrachloride (1 c.c.) was added to a solution of 2-acetoxy-3,4,4′-trimethoxychalcone (0·6 g.) in carbon tetrachloride (15 c.c.). After 2 hr. at room temperature the solution was evaporated under reduced pressure, and the residue was boiled with 1 : 4 aqueous acetone (10 c.c.) for 13—15 min. The solution was extracted with ether, and the ethereal solution was washed with water and then dried ($MgSO_4$). The *bromohydrin* crystallised from the filtered ethereal solution, and recrystallisation from benzene–hexane gave prisms, m. p. 138—145° (Found: C, 53·4; H, 4·8. $C_{20}H_{21}BrO_7$ requires C, 53·1; H, 4·7%). The bromohydrin was boiled with 10% aqueous sodium carbonate (8 c.c.) for 3 min. and then poured into water (50 c.c.). The precipitate was collected when solid, and crystallisation from ethanol (charcoal) gave *dihydro*-7,8,4′-*trimethoxyflavonol* (0·15 g., 28%), m. p. 172° (Found: C, 65·7; H, 5·6. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5%). The dihydroflavonol was also prepared, without isolation of the bromohydrin, by adding aqueous sodium carbonate to the aqueous-acetone solution of the chalcone dibromide after the heating period.

(±)-7,8,4′-*Trimethoxy*-2,3-trans-*flavan*-3,4-cis-*diol*.—(*a*) Sodium borohydride (0·6 g.) was added to an ice-cold solution of the dihydroflavonol (2 g.) in methanol (*ca.* 150 c.c.), the solution was acidified with acetic acid after 24 hr., and the solvent was then removed under reduced pressure. The residual diol was dried over potassium hydroxide; it then crystallised from methanol in needles (1·3 g., 65%), m. p. 83—84°, raised to m. p. 126—127° by being dried *in vacuo* at 50° over phosphoric oxide (Found: C, 64·6; H, 6·2. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%). The *isopropylidene derivative* (76%) (prepared as described for the melacacidin analogue [6]) crystallised from methanol in needles, m. p. 168—169° (Found: C, 67·6; H, 6·6. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%).

(*b*) Dihydro-7,8,4′-trimethoxyflavonol (0·2 g.) in methanol (20 c.c.) was hydrogenated over Adams catalyst (0·01 g.) for 12 hr. at 50°/70 atm. The filtrate from the catalyst was evaporated under reduced pressure, and crystallisation of the residue from ethanol gave the diol (0·13 g., 65%) in colourless needles, m. p. 96—100° raised to m. p. 126—127° by drying at 50° over phosphoric oxide *in vacuo*. It did not depress the m. p. of the diol prepared by method (*a*).

(+)-*Inositol from* (+)-*Pinitol*.—(+)-Pinitol from *A. intertexta* had m. p. 184—185°, $[\alpha]_D^{25}$ +65° (3% in H_2O) (lit.,[13] m. p. 186—188°, $[\alpha]_D^{25}$ +65·5° in H_2O). Paper chromatography of the reaction mixture showed that conversion of pinitol (R_F 0·23) into inositol (R_F 0·14) occurred rapidly in boiling 6N-hydrochloric acid, and was complete in 8 hr.; no other product was detected with the alkaline silver nitrate spray. (+)-Pinitol (5 g.) was boiled with 6N-hydrochloric acid for 8 hr. and the pale brown solution was evaporated to dryness on a steam-bath. The residue was re-evaporated with water twice to remove acid, and then with ethanol, which left a crystalline residue (4·75 g.), m. p. 194—221°. Recrystallisation from aqueous ethanol gave (+)-inositol as prisms (4·1 g., 88%), m. p. 236—238° raised by recrystallisation to m. p. 239—240°, $[\alpha]_D^{16}$ +64° (1·2% in H_2O) (Found: C, 39·8; H, 6·7. Calc. for $C_6H_{12}O_6$: C, 40·0; H, 6·7%). Stephen [9] records m. p. 244° and $[\alpha]_D^{28}$ +66·2° (1·21% in H_2O) for (+)-inositol obtained by demethylation of (+)-pinitol with hydriodic acid.

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[13] Karrer, "Konstitution und Vorkommen der organischen Pflanzenstoffe," Birkhäuser Verlag, Basle, 1958, p. 117.

100. *An Infrared Spectroscopic Investigation of Nucleic Acid Constituents.*

By C. L. Angell.

The infrared spectra of cytosine, uracil, adenine, and guanine, of ribose and deoxyribose nucleosides derived from these bases, and of some mononucleotides have been examined in the solid state between 4000 and 650 cm.$^{-1}$. Many of the prominent absorption bands have been assigned to vibrations of structural groups with the help of spectral data from a number of derivatives, including those in which the labile hydrogen atoms have been replaced by deuterium. The infrared evidence confirms the view that in the solid state cytosine and guanine exist in the keto-amino-form, adenine in the amino-, and uracil in the diketo-form. Evidence is presented that the cytidine and adenosine phosphates exist in zwitterionic forms in the crystalline state.

Great interest in the nucleic acids and their constituent molecules—heterocyclic nitrogenous bases, nucleosides and nucleotides—has led to a number of structural investigations by physical methods; infrared spectroscopy has played a prominent rôle in this work. Such spectra have been published previously for derivatives of the pyrimidine [1] and purine bases,[2] and for nucleosides,[3] nucleotides,[4] and nucleic acids [5] in the solid state. In a number of cases infrared methods have also been used to study these compounds in solution in heavy water.[6]

In the present work spectra of substituted derivatives of the relevant bases (where often only one tautomeric form is possible), of all the ribose and deoxyribose nucleosides, and of a number of nucleotides were obtained. In addition, the labile hydrogen atoms of the four bases and of the corresponding ribose nucleosides were exchanged with deuterium and the spectra of these " deuterated " compounds measured.

The spectra were studied with the following principal aims: (1) to confirm the tautomeric structures of the bases; (2) to make assignments of absorption bands to vibrations of structural groupings where this is possible; (3) to note any spectral changes in the series, base ⟶ nucleoside ⟶ nucleotide; and (4) to differentiate if possible between (*a*) ribose and deoxyribose derivatives and (*b*) the 2′- and 3′-phosphates of nucleosides.

Experimental

Materials.—The majority of compounds investigated were obtained from members of the Chemical Laboratory, Cambridge University, or from Professor Sir Alexander Todd's personal collection of chemicals. Others were obtained from the following sources: isocytosine (Dr. R. Markham, Molteno Institute, Cambridge); 1,3-dimethyluracil (Genatosan Ltd., Loughborough); purine, 9-methylpurine, and 2-hydroxypyrimidine (Professor A. Albert, Australian National University); and adenine hydrochloride (L. Light and Company Ltd., Colnbrook, Bucks.).

Cytosine, adenosine, and guanosine crystallise with water of crystallisation; anhydrous samples were obtained by drying them under a vacuum at about 110° for several hours. The hydrochlorides of the bases were obtained as cytosine,HCl,H_2O, adenine,HCl,$\frac{1}{2}H_2O$, and guanine,HCl,H_2O, and were used as such.

The technique used for the deuterium exchange of labile hydrogen atoms was as follows: about 10 mg. of a substance were gently refluxed with 0·4 c.c. of heavy water for 0·5 hr.; the

[1] Short and Thompson, *J.*, 1952, 168; Brown and Short, *J.*, 1953, 331.
[2] Willits, Decius, Dille, and Christensen, *J. Amer. Chem. Soc.*, 1955, **77**, 2569; Lacher, Bitner, Emery, Seffl, and Park, *J. Phys. Chem.*, 1955, **59**, 615.
[3] Blout and Fields, *J. Amer. Chem. Soc.*, 1950, **72**, 479; Fraser, Ph.D. Thesis, London, 1952.
[4] Harris, Orr, Roe, and Thomas, *J.*, 1953, 489; Blout and Fields, *J. Biol. Chem.*, 1949, **178**, 335.
[5] Fraser and Fraser, *Nature*, 1951, **167**, 759; Sutherland, *Rend. Ist. Lombardo Sci. Lettere, Classe Sci.*, 1955, **89**, 67; Sutherland and Tsuboi, *Proc. Roy. Soc.*, 1957, *A*, **239**, 446.
[6] Miles, *Biochim. Biophys. Acta*, 1956, **22**, 247; 1958, **27**, 46; Lenormant and Blout, *Compt. rend.*, 1954, **239**, 1281; Blout and Lenormant, *Biochim. Biophys. Acta*, 1954, **15**, 303; Lenormant and deLozé, *Bull. Soc. chim. France*, 1955, 1501, 1504; Sinsheimer, Nutter, and Hopkins, *Biochim. Biophys. Acta*, 1955, **18**, 13.

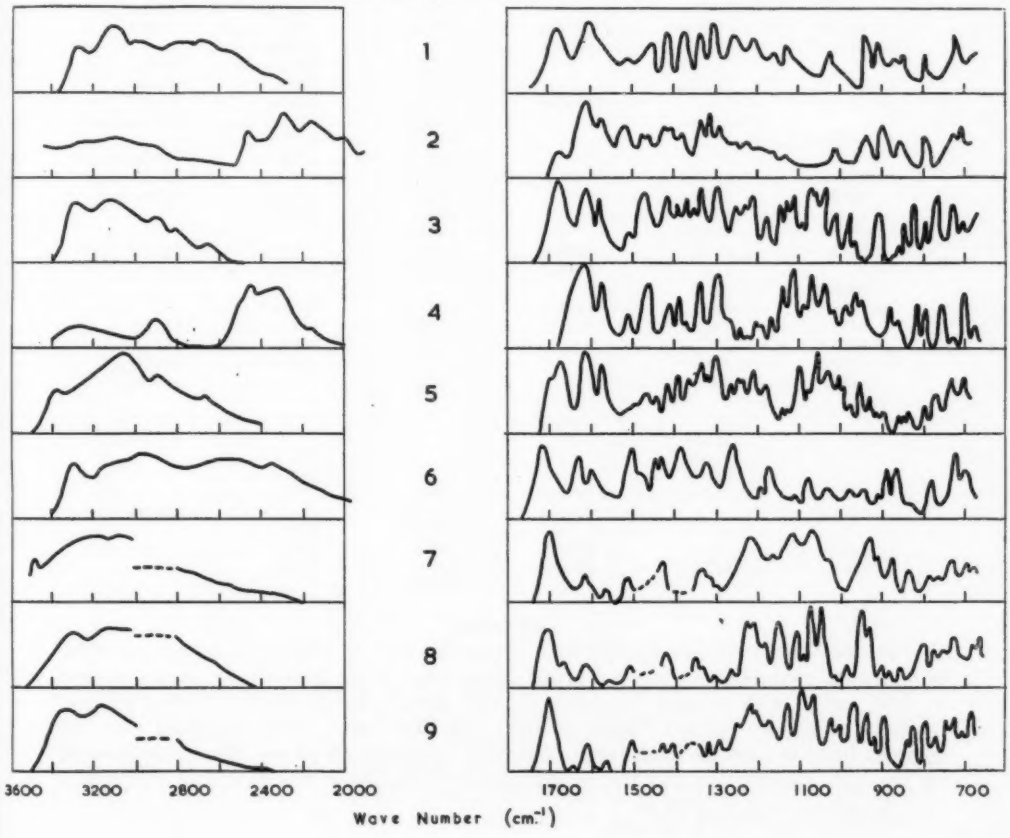
solution then was evaporated to dryness and the residue used to make up a mull in Nujol by the usual technique. All these operations were carried out in a dry-box. The heavy water used was a Norsk Hydro-Electrisk (Norway) product and contained 99·70% of D_2O.

TABLE 1. *List of additional spectra studied.*

D-Ribose	9-Methylpurine	Thymidine diphosphate Ba salt
Deoxy-1-ribose	9-Methyladenine	Thymidine-3′ phosphate Ba salt
2-Hydroxypyrimidine	Guanine hydrochloride	Thymidine-5′ phosphate Ba salt
6-Methoxy-3-methyl-2-pyrimidone	Deoxy-5-methylcytidine hydrochloride	5′-Acetyladenosine
6-Dimethylamino-3-methyl-2-pyrimidone	Adenine picrate	5′-Acetyldeoxyadenosine
3-Methylcytosine	Adenosine picrate	3′-Acetyldeoxyadenosine
1,3-Dimethylcytosine	Deoxyadenosine picrate	3′,5′-Diacetyladenosine
Cytosine-*N* benzyl phosphate	Cytidine-2′ benzyl phosphate	3′,5′-Diacetyldeoxyadenosine
Isocytosine	Cytidine-3′ benzyl phosphate	2′,3′,5′-Triacetyladenosine
4-Methyluracil	Cytidine-3′ methyl phosphate	3′-Acetylthymidine
3-Methyluracil	Adenosine-5′ benzyl phosphate	5′-Acetylthymidine
Purine	Adenosine diphosphate Ba salt	3′-Acetyldeoxyguanosine
	Uridine-2′,3′ phosphate Ba salt	3′,5′-Diacetyldeoxyguanosine
	Guanosine-2′,3′ phosphate Ba salt	

Spectra.—These were obtained on a Perkin–Elmer Model 21 double-beam spectrometer with a sodium chloride prism and a Hilger D209 spectrometer and calcium fluoride and sodium

Infrared spectra of: (1) *adenine*, (2) *deuterioadenine*, (3) *adenosine*, (4) *deuterioadenosine*, (5) *deoxyadenosine*, (6) *adenine hydrochloride*, (7) *adenylic acid* a, (8) *adenylic acid* b, (9) *adenosine-5′ phosphate*.



chloride prisms. The majority of the spectra were taken as Nujol and hexachlorobutadiene mulls and some in KBr discs. A number of the spectra were obtained from the collection of infrared spectra at the Chemistry Laboratories, Cambridge, and some of these (five adenosine nucleotides [7] and six cytidine nucleotides [8]) have already been published. These known spectra were used in their original (full-size) form in the present work for the assignment of bands.

The spectra of a representative series of compounds are presented in the Figure for the region 4000—650 cm.$^{-1}$; the frequencies of these and other compounds are listed in Tables 2—6. A list of related compounds for which spectra were also available is given in Table 1. Data for these compounds were used in assignments and comparisons.

TABLE 2. *Cytosine derivatives.*

Cytosine	Deuterio-cytosine	Cytosine HCl	Cytidine	Deuterio-cytidine	Deoxy-cytidine
700w		697m		694w	
	718w	733w	714m	720w	717m
		755s	757w	745w	752w
	771w			775w	
784w	787s	782w			786w
794s		787w	791s	790s	792s
823m		825s	818s	810m	
	851w	850w	855m	845m	860w
	864w	885s	872m	855m	899w
				917m	931w
966w	968w		944m	960m	960m
995w	978w	976m	985m	980w	993m
1011w	1006w	1005m		1003m	
			1036w	1040m	1047s
	1046w		1054s	1063s	1057w
		1105w	1098m	1080m	1096w
	1118m		1136w	1115m	1115m
1156w	1178w		1153w	1170w	
			1192w	1183w	1176w
1236s	1235w	1228s	1212m		1213w
1275s	1279m		1247w	1255m	1279s
			1290s	1295s	
	1312m		1309w		
1362s	1374s	1370w	1342w		1356w
	1416w	1414s	1400w	1396m	1397w
1458s					
1506w	1502s	1497m	1504s	1500s	
1538m	1548w	1543s	1543m	1515w	1527w
1621w	1605s		1607s	1608s	1618s
1655w	1637s			1640s	1642w
1667s	1680w		1653s		1667m
		1682s			
		1736s			
	2123s				
	2155s			2427s	
	2320s			2564m	
1667m	2525s	2630w	2725w	2725w	
2778m		2899m	2915m		2940m
			3085m	3077w	
3155s		3105m	3225s	3205w	3106s
3367s	3278w	3355w	3333s	3333w	3370s
			3448m		

DISCUSSION

Cytosine Derivatives.—In the spectrum of cytosine itself (6-amino-2-hydroxypyrimidine or 6-amino-2-pyrimidone) there is a broad strong band in the double-bond region centred at 1667 cm.$^{-1}$ with several shoulders on the low-frequency side. 3-Methylcytosine, however, gives two distinct bands, at 1626 and 1667 cm.$^{-1}$. It is supposed that the complex band of cytosine itself results from the superposition of two absorptions caused by the NH_2 deformation and the conjugated C=O stretching vibration. In derivatives

[7] Brown and Todd, *J.*, 1952, 44.
[8] Michelson and Todd, *J.*, 1954, 34.

where the amino-group is removed or substituted, this band moves to a lower frequency: *e.g.*, deuteriocytosine 1637 cm.$^{-1}$, 2-hydroxypyrimidine (2-pyrimidone) 1644 cm.$^{-1}$, and 6-dimethylamino-3-methyl-2-pyrimidone 1645 cm.$^{-1}$. This shows that the carbonyl frequency is at about 1640 cm.$^{-1}$ and that the NH_2 vibration in cytosine is at a somewhat higher frequency. In 1,3-dimethylcytosine the conjugation of the carbonyl group is removed, and the carbonyl band moves to 1681 cm.$^{-1}$. These results and those in the 3000 cm.$^{-1}$ region discussed below confirm the structure of cytosine as that of a 2-pyrimidone derivative, as has been suggested previously on infrared evidence. Another weaker band in the 1600—1640 cm.$^{-1}$ region usually appearing with derivatives of cytosine and other 2-pyrimidones is assigned to a ring vibration (probably mainly coupled C=N stretching modes). This band is characteristic of the pyrimidone ring system as a whole, for it is not present in 1,3-dimethylcytosine or in uracil derivatives which have no ring C=N bonds.

In the region 1535—1550 cm.$^{-1}$ many cytosine derivatives show a strong band which seems to be characteristic of the pyrimidone structure: 2-hydroxypyrimidine (2-pyrimidone) gives the frequency 1545 cm.$^{-1}$, and 4-hydroxypyrimidine (4-pyrimidone) 1541 cm.$^{-1}$. This band is most reasonably assigned to an N–H in-plane deformation vibration. The band at 1538 cm.$^{-1}$ in the spectrum of cytosine is removed on deuteration, and becomes

TABLE 3. *Cytidylic acids.*

Cytidine HCl	Deoxy-cytidine HCl	Cytidylic acid *a*	Cytidylic acid *b*	Cytidine-5′ phosphate	Deoxy-cytidine-3′ phosphate	Deoxy-cytidine-5′ phosphate
703w	711w	671w	666m	681w		
723m	721m	728m	725w	717m	730w	727w
752w	746m	755w	743w	755w		752w
		762w	755w			770w
784w	772s	779w	777m	773w	778w	787w
816w	788w	797m	790w	786w	800w	
830s	832w	844w		808m	830w	806m
864w	847s	874w	854m	837w	857w	866w
873w		881w	896w	870w	897w	888w
915m		914m	914w	905w		
		926m	939w	931m	935w	927s
983m	957m	973w	969s	988m	966m	980m
993m	1026w	1002w		1016w	1013m	1030m
1045m	1042w	1044w	1042m	1048s		1038m
1081m		1069s	1075s	1069m	1058m	1060s
1093w	1087s			1093m	1093m	1093w
1117s	1129m	1108m	1108w	1111m		
	1143w	1124s	1150s	1161m	1156m	1156w
1188m	1183w	1181w	1190w		1195w	1196w
1239m	1228m	1209m	1227w	1222m	1235w	1227m
1278s	1271s	1266m	1261w	1255w	1258w	1259w
1293w	1285m	1277m	1280m	1279m	1282s	1288m
1333w	1311w	1309w	1307w	1333w	1324w	1333w
	1349w	1351w	1330w	1351w	1351w	1355w
1396w	1420w	1418w	1414w		1408m	
1538s	1538s	1536m	1538m	1545m	1538s	1553m
				1605w		1600w
			1647m	1626w	1647w	
1681s	1675s	1721s	1695s	1704s	1686m	1698m
1724s	1715s	1748m	1724s	1724s	1730m	1733s
3096s	3086m	3090m				
	3215m	3225m		3125w		3120w
3300s	3333s	3300m	3246m	3300m	3320s	3333w
3448m				3570w		

very weak in the spectra of 3-methylcytosine, cytidine, and deoxycytidine, all of which have the hydrogen atom of $N_{(3)}$ substituted. In the spectrum of deuteriocytosine a new band appears at 1118 cm.$^{-1}$, giving an isotopic ratio of 1·375. Strong evidence in favour of the origin of this band in a principally hydrogen deformation vibration is found in the fact that the hydrochlorides of cytidine and deoxycytidine give a strong band in this region. In these compounds the additional proton is added to $N_{(1)}$ and thereby re-establishes a

XUM

secondary amide group. This band also appears in the same region in the spectra of all the guanine derivatives.

There is a strong band near 1275 cm.$^{-1}$ in the spectrum of cytosine and all cytosine derivatives. But it is not present in those of 2-hydroxypyrimidine (2-pyrimidone) or 6-methoxy-3-methyl-2-pyrimidone where the external amino-group is missing. This band is therefore attributed to the external C–N bond, as assignment in good agreement

TABLE 4. *Uracil derivatives.*

Uracil	Deuterio-uracil	5-Methyl-uracil	1,3-Di-methyl-uracil	Uridine	Deuterio-uridine	Deoxy-uridine	Thymidine	Uridylic acid
			683m	715w	720w		723w	673w
	733w	740m	728w	752w	743w	734w	734w	732w
760m	765s	762s	762s	766s	766s	766s	758s	760w
781w				775w	786w		766m	
807w			800w	807w	806s		792w	810w
822s	820s	815s	816s	831s	828s	830w		833m
851m		845s		853w	853w	863m	851m	869w
	882m			877w	897w		870w	891w
	965w	935m	931w	953m	969m	934w	957m	
994s	980s	983m	966w	982m		960m	971m	973m
1004s			1004w	1005w	1010s	998m	1008m	997s
		1029m		1035w		1042m	1025w	1020m
		1048w		1054s	1056s	1056m		1042m
				1075m	1075w	1073w	1064s	1075w
1099w				1099s	1105s	1100m	1096m	1101w
	1140s		1136m	1136w	1130w	1112w	1120m	1124m
	1165w		1172m	1172w	1183w	1167m	1170w	
		1205s						1203w
1238s	1230w	1244s	1230m	1211m	1239m	1221w	1221m	1247w
			1261w	1269s	1264w	1259s	1270s	1260m
	1310w			1323w	1287m	1288w	1316m	1282s
	1330s	1366w	1340s	1366m	1326w		1362m	1314w
1389m	1390w	1381m	1377m	1398m	1393m		1400m	1379s
1418s	1422w	1422s	1400s	1424m	1416w		1435s	1412w
1451s	1475s	1447s	1437s	1475m	1460m		1475s	1466s
		1484m	1480m					
1508m		1495m					1515w	
	1565w		1587w		1610m	1618w		
1666m	1640s		1655w		1647s	1664m	1661s	
1681m		1681s	1664s	1686s	1686s	1681s		1686s
1724s	1712s	1739s	1709w			1695w	1709s	1724s
1745w	1740w	1785w		1788w				
	2135w							
	2268s				2326m			
	2400w				2475s			
		2800w		2810w			2833m	
2924m		2920m	2940w	2933m	2915m		2967m	2915m
				2985m			3000m	
3080s	3065m	3020s	3077w		3086m		3077w	3077w
		3170m		3125m		3125m	3155w	3185s
				3340s	3333s		3300s	3415m

with that given by Bellamy [9] for the C–N stretching vibration in primary aromatic amines.

In the region 780—800 cm.$^{-1}$ all cytosine derivatives exhibit a strong and sharp band. These bands are very similar to those due to out-of-plane hydrogen deformation vibrations in the case of substituted benzene derivatives and olefins, and they probably arise from this type of vibration. In the spectrum of cytosine itself there is also a broad band at 823 cm.$^{-1}$ which may be assigned to an out-of-plane vibration of the hydrogen atom on $N_{(3)}$ because it is removed both by deuteration and by replacement of this hydrogen by a methyl group. It is well known that out-of-plane N–H or O–H vibrations usually give characteristically broad bands in the low-frequency region.

Deuteration causes significant changes in the 1400—1600 cm.$^{-1}$ region of the spectrum

[9] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954.

of cytosine, indicating that vibrations usually considered to involve doubly-bonded and conjugated heavy atoms include considerable contributions from hydrogen vibrations. Actually the spectra of deuteriocytosine and cytidine closely resemble each other in the absence of the strong band found at 1458 cm.$^{-1}$ in cytosine, and the appearance of others at 1503 and 1605 cm.$^{-1}$. These changes are probably associated with the removal of the hydrogen atom from $N_{(3)}$ and hence very little further change is observed in this region on deuteration of cytidine.

An examination of the 3000 cm.$^{-1}$ region provides confirmation that cytosine and its

TABLE 5. *Adenine derivatives.*

Adenine	Deuterio-adenine	Adenosine	Deuterio-adenosine	Deoxy-adenosine	Adenine HCl	Adenylic acid *a*	Adenylic acid *b*	Adenosine-5′ phosphate
	708m	705w	704s	703m	702w	696w	677w	683m
722m	720w	722m	730w	728m	718m	724w	723m	725m
		767m	756s	770m	776m	778w	775m	737m
797m	796m	795w	796m	796w			796m	787m
		823m	812s	837w		825w	849w	822m
847m	855w	844m	858w	858w	858m		869w	831w
870w		860w	877s	897w	888m	868w	879w	893w
911m	896m	903s		906w	904w	904w	926m	913w
938m	935m		948m	930w	937w	923m	941s	930m
		978m	962s	950m				966s
			980m	977w	974w		975m	
1022m	1010w	1011m	1020w	1006m	1024w	1020w		1020w
		1037s	1036s	1028m	1036w	1059m	1042s	
		1054m	1067s	1054s	1072w		1070s	1064s
		1071m	1085w	1099s				1089s
1124m	1130w	1107m	1111s	1123w	1105w	1108w	1100m	1114m
1155w	1156w	1142w	1134m	1158w		1154w	1143m	
	1183w	1176w	1163w	1180w	1171m		1186w	1170w
1206m		1208m	1200w	1209m		1213m	1218s	1219m
	1226w	1225w	1235w	1233w				
1250m	1250w	1250w	1261w	1264w	1258s		1259w	1250w
	1285m		1290s					
1305m	1310s	1300s		1300s			1304w	1294w
1333m	1335s	1333m	1332s	1324m	1319w	1324w	1328w	1317w
		1351w	1370w	1339m			1340m	1345w
1368w	1375m	1370w	1383m	1366w	1381m			
	1410m	1387w	1402w	1390w				1402w
1418m	1420m	1414s		1418w	1425w	1422w	1416m	1422w
1451w	1460m		1460m	1447w	1441w			
	1475m	1470s		1473w				
1510w	1510s		1510m	1515w	1500m	1507w	1504w	1500m
	1575s	1575m	1572s	1574s	1597m	1555w	1553w	1562w
1605m	1610s	1608m	1623s	1612s	1623s	1607w	1615s	1613m
1672s	1673w	1672s		1672s	1712s	1691s	1706s	1700s
	2155m							
	2288s		2320s					
	2463m		2457s		2565w			
2680w		2667w	2500w	2680w				
2780w		2825w						
		2900m	2920w	2915m				
3000w					2958m			
3105s	3096w	3125s		3067s		3075s	3125m	3155s
3280m		3300s	3300m	3378w	3280m	3225s	3300m	3350m
						3480w		

derivatives exist as amino-forms. Cytosine, 3-methylcytosine, cytidine, and deoxycytidine all give two strong bands in this region which on deuteration shift to lower frequencies as follows:

cytosine	3155 and 3367 cm.$^{-1}$ to 2320 and 2525 cm.$^{-1}$
3-methylcytosine	3130 and 3333 cm.$^{-1}$
cytidine	3225 and 3333 cm.$^{-1}$ to 2427 and 2564 cm.$^{-1}$
deoxycytidine	3106 and 3370 cm.$^{-1}$

These frequencies are in good agreement with those of aromatic amino-compounds where

the presence of the amino-group is certain *e.g.*, α-naphthylamine [10] (3230 and 3330) and 5-aminopyrimidine (3180 and 3345). 1,3-Dimethylcytosine gives only one strong band in this region, at 3268 cm.$^{-1}$; this can be assigned to the imino(NH)-group.[11]

If the transition from cytosine to the two nucleosides is considered, very little change occurs in those parts of the spectra due to the cytosine residue, but a number of strong bands appear between 1000 and 1200 cm.$^{-1}$ which are due to the sugar molecules. When, however, the transition is followed from the nucleosides to the nucleotides, quite considerable changes in the spectra are evident; these changes closely parallel those occurring on passing from cytosine or the nucleosides to their hydrochlorides. Instead of the 1667 cm.$^{-1}$ band of cytosine, the hydrochlorides show two strong bands in the ranges 1675—1682 cm.$^{-1}$ and 1715—1736 cm.$^{-1}$, while the cytidylic acids have two bands at 1686—1720 cm.$^{-1}$ and 1724—1748 cm.$^{-1}$. These bands are assigned as NH_2 deformation and C=O stretching vibrations respectively. Other similarities between the spectra of the hydrochlorides

TABLE 6. *Guanine derivatives.*

Guanine	Deuterio-guanine	Guanosine	Deuterio-guanosine	Deoxy-guanosine	Guanylic acid
689m	687w	678m	665w	678m	
703m	702w		697br		692w
727w	721w	733w	726w	723w	
776s	776m	778s	777m	778s	780m
789w		800w	807w	800w	
	825w	827w			839w
851s	850m			870w	848w
877m	876w	882w	870w	890w	
	912w	910m	900w		917sh
949s	948w	935w		932m	930w
		978w	980s	993w	976s
				1029w	1030m
1042w		1036m	1042s	1058m	1057m
		1078s	1093s	1095m	1078s
1120m	1120w	1118m			1127s
1172s	1167m	1167w		1171m	1176m
1215w	1215w	1227w			
1263s	1261w		1263w	1245w	1235w
	1307w	1317m	1302m	1324sh	
	1337w	1337m	1348w	1368sh	1355w
1375s	1364s	1393m		1393m	1380w
1418m	1416w	1422m	1404w		1416w
1464w	1460m		1456w		1455w
1477m	1475m	1486s		1488m	1481w
1555s		1538m	1534s	1538m	1538w
1567s	1565m	1575w	1575s	1595sh	
	1616s	1613sh		1608s	1608m
1639w		1631m		1637s	
1681s	1678s		1680m		
1701s	1695s	1736m	1704m	1733s	1698s
	2114m		2075m		
	2278s		2370m		
	2494s		2500s		
2680s	2688m	2703m		2703w	
2840s	2872m	2833w	2900m	2857sh	
3077s	3086m			2924m	
		3175m		3185s	3150m
3310s	3300s	3280m	3330w	3310s	3425s

and the cytidylic acids show that the same changes in the cytosine nucleus occur in the two types of compound. Since in the hydrochlorides a proton is added to the $N_{(1)}$ atom, this must also occur in the case of the cytidylic acids. It is concluded, therefore, that all the cytidylic acids exist in a zwitterion form in the solid state, one of the hydrogen atoms from the phosphate group having moved to the cytosine residue. Such zwitterion

[10] Flett, *J.*, 1948, 1441.
[11] Angyal and Werner, *J.*, 1952, 2911.

formation has already been suggested to exist in solution,[12] but the present infrared results appear to be the first to present strong evidence for the existence of zwitterions for nucleic acids in the solid state.

Uracil Derivatives.—In the case of uracil the bond distances for the two C–O bonds obtained from *X*-ray evidence [13] clearly indicate that the molecule exists in the diketo-form, *i.e.*, as 1,2,3,4-tetrahydro-2,6-dioxopyrimidine; strong supporting evidence for this structure for uracil derivatives comes from the examination of the infrared spectra in the double-bond region.[1] Uracil and each of its methyl-substituted derivatives show two strong bands in this region, and these have been assigned by Randall *et al.*[14] to the 4- and 2-keto-groups. While these bands are rather ill-defined for the solid, in the case of 1,3-dimethyluracil they could be satisfactorily resolved in solution (in $CHCl_3$ at 1660 and 1703 cm.$^{-1}$, in CCl_4 at 1670 and 1710 cm.$^{-1}$, and in C_6H_6 at 1670 and 1707 cm.$^{-1}$). The position of these bands seems to be characteristic for the grouping –NH·CO·NH·CO– in a six-membered ring containing a carbon–carbon double bond (see also xanthine and caffeine [14]). The band of moderate intensity at about 1500 cm.$^{-1}$ in uracil and its 5- and 4-methyl derivatives is considered to correspond to the band in the same region in the cytosine derivatives, *i.e.*, an N–H in-plane deformation vibration. On deuteration of uracil this band is removed and a new band appears at 1140 cm.$^{-1}$ (ratio 1·32).

There are two strong bands in the spectra of all uracil derivatives in the regions 1415—1440 cm.$^{-1}$ and 1450—1490 cm.$^{-1}$, respectively. These are assigned principally to vibrations of the uracil nucleus but shifts on deuteration suggest that they are partially coupled with some N–H vibration. The second of these bands shifts by about 20 cm.$^{-1}$ in the same direction on deuteration as when the $N_{(3)}$ atom is otherwise substituted (3-methyluracil 1486 cm.$^{-1}$, uridine 1475 cm.$^{-1}$).

In all the uracil derivatives there are two strong, sharp bands at about 760 and 820 cm.$^{-1}$. They are not affected by deuteration or by substitution of both N–H groups. They may correspond to out-of-plane C–H vibrations and seem to be very characteristic of the tetrahydro-2,6-dioxopyrimidine structure. There are two additional broad bands in the spectrum of uracil, at 807 and 851 cm.$^{-1}$. These are assigned to the two out-of-plane NH deformation vibrations because they are absent in the spectrum of deuterio-uracil; they are present in 4-methyluracil, but one of them is removed in 3-methyluracil and both of them are removed from the spectrum of 1,3-dimethyluracil.

The 3000 cm.$^{-1}$ region shows a strong band for uracil and its methyl-substituted derivatives between 3050 and 3150 cm.$^{-1}$. By comparison with spectra for phthalimide (3205 cm.$^{-1}$) and succinimide (3145 cm.$^{-1}$) these bands can be satisfactorily assigned as N–H stretching vibrations of the –CO·NH·CO– grouping. The other NH fundamental probably contributes to this absorption band. On deuteration of uracil this band shifts to 2268 cm.$^{-1}$. 1,3-Dimethyluracil gives only two weak bands, at 3077 and 2940 cm.$^{-1}$, which are probably due to unsaturated and methyl C–H stretching vibrations, respectively.

There is very little change in the spectrum due to the uracil nucleus when a sugar group is added. Uridine and deoxyuridine show only one broad band in the 1700—1600 cm.$^{-1}$ region, but it seems probable that this would be resolvable if the compounds could be examined in solution. A number of strong bands appear in the region 900—1100 cm.$^{-1}$ which are characteristic of the sugar residue.

For uridylic acid *b*, again very little change is found on the addition of the phosphate group to uridine. This is in agreement with expectation, since in this case zwitterion formation is much less likely. The similarity of the spectra of uracil and its nucleosides and nucleotide suggests that in these more complex compounds the uracil is also present in the diketo-form.

[12] Cavalieri, *J. Amer. Chem. Soc.*, 1952, **74**, 5804.
[13] Parry, *Acta Cryst.*, 1954, **7**, 313.
[14] Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," D. van Nostrand Co., New York, 1949.

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Adenine Derivatives.—Since infrared evidence strongly suggests that adenine (6-amino-purine) exists in the amino-form and it would be expected that the structure of the purine nucleus would not be significantly affected by the addition of the amino-group, an attempt was made to correlate bands in the spectra of adenine and purine. However, it was found that there was little resemblance between the two spectra except for the presence of two strong bands at 1575 and 1610 cm.$^{-1}$. These two bands are very characteristic of the purine nucleus (or the pyrimidine ring; pyrimidine [1] has bands at 1570 and 1610 cm.$^{-1}$) and are given by all adenine derivatives (including the six acetyl-substituted adenosines) in the narrow frequency ranges 1575 $\pm$ 5 and 1610 $\pm$ 10 cm.$^{-1}$. The first of these bands appears only as an unresolved shoulder in the spectrum of adenine itself but is clearly present in those of deuterated adenine and 9-methyladenine.

Evidence for the amino-form can be found in the bands at 1672 cm.$^{-1}$ in the spectra of adenine, adenosine, and deoxyadenosine, which can without doubt be assigned to an NH_2 deformation vibration. They are removed on deuteration and are in approximately the same position as the corresponding bands in the spectra of fourteen aminopyrimidine derivatives [1] (including 5-aminopyrimidine, which cannot have any other tautomeric form). In contrast to the cases of cytosine and uracil, deuteration causes few changes in the spectra of adenine and adenosine, except for removal of the 1672 cm.$^{-1}$ band and appearance of a new one at 1510 cm.$^{-1}$ with both compounds, and another at 1285 cm.$^{-1}$ for adenine and at 1290 cm.$^{-1}$ for adenosine. The first of these is probably a shifted skeletal vibration and the second is assigned to the ND_2 deformation vibration (ratio 1·30), even although its intensity in deuterioadenine is less than would be expected.

In the region 1300—1500 cm.$^{-1}$ the spectrum of adenine resembles that of 9-methyl-purine more than that of purine itself. A series of five fairly strong bands of adenine in this region can also be found in the spectrum of 9-methylpurine and of all the adenine derivatives in approximately the same positions. The strongest of these, near 1305 cm.$^{-1}$, is very characteristic of these compounds. None of these bands is affected by deuteration. The broad band at 870 cm.$^{-1}$ in the spectrum of adenine is assigned to the out-of-plane deformation vibration of the $N_{(9)}$–H; it is removed on deuteration and by $N_{(9)}$-methylation. A broad band in the same position can also be found in the spectrum of purine but is absent from that of 9-methylpurine.

Addition of the ribose or deoxyribose unit to the adenine molecule does not cause any changes in the characteristic features of the spectrum due to the adenine part, but once again a number of strong bands appear in the region 950—1150 cm.$^{-1}$ which are due to the sugar residues. Very considerable changes, however, occur in the spectra when a phosphate group is added to the adenine nucleosides; these changes are closely parallel to those which occur when a proton is added to the adenine nucleus.

The structure of adenine hydrochloride has been determined by *X*-ray crystallography,[15] and the extra proton was found to be located on the $N_{(1)}$ atom. It would be expected that the charge distribution and bond orders for the $(adenine,H)^+$ ion would be somewhat different from those existing in the adenine molecule and that changes might well occur in the infrared spectrum. The most outstanding of these changes observed is the shift of the NH_2 deformation vibration from 1672 cm.$^{-1}$ in adenine to 1712 cm.$^{-1}$ in the hydrochloride (the picrate has this band at 1704 cm.$^{-1}$ and the sulphate [14] at 1698 cm.$^{-1}$). From the direction of the shift it is clear that we are dealing, not with an NH_3^+ unit, but with a NH_2 group affected by the addition of a neighbouring positive charge. In the spectra of all the adenine nucleotides the corresponding band is in the region 1690—1710 cm.$^{-1}$. It is, therefore, suggested that in the adenylic acids the adenine part has virtually the same molecular and electronic structure as in adenine hydrochloride. This implies that there is probably a proton on the $N_{(1)}$ atom and that the adenylic acids exist in a zwitterion form.

[15] Cochran, *Acta Cryst.*, 1951, **4**, 92.

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Other marked changes can also be observed in the spectra of adenine,HCl and the adenylic acids in the region associated with the aminopurine unit. For example, the band at 1605 cm.$^{-1}$ in adenine has lost intensity considerably, and the band at 1572 cm.$^{-1}$ has disappeared completely, giving place to a very weak band at 1550—1560 cm.$^{-1}$ in the adenylic acids. On the other hand, a new band appears near 1500 cm.$^{-1}$, strong in the spectrum of adenine,HCl and weaker in the adenylic acids. Gone also is the outstanding band at 1305 cm.$^{-1}$, and the region 1300—1500 cm.$^{-1}$ shows only weak bands in the spectrum of adenylic acid *b* hydrate (the only adenine nucleotide examined in hexachlorobutadiene also). Since most of these bands were probably associated with stretching vibrations of the adenine derivatives, the above changes indicate considerable changes in the electronic distribution within the adenine nucleus. It should be mentioned that in the case of the six acetyl-substituted adenine nucleosides (where the acetyl groups are in corresponding positions to the phosphate groups) no such changes in the spectra occurred. All six of these compounds have strong bands at 1667—1682 and 1605—1613 cm.$^{-1}$ and a band of medium intensity at 1574—1584 cm.$^{-1}$ as for adenine itself. Since the introduction of one or more acetyl groups into the sugar residue of adenosine cannot lead to zwitterion formation, these data lend additional support to the hypothesis of zwitterion formation in the case of the adenylic acids.

In the 3000 cm.$^{-1}$ region adenine and the two nucleosides each show two strong bands at about 3100 and 3300 cm.$^{-1}$ which are shifted on deuteration to lower frequencies. These bands are characteristic of aromatic amines, and their presence strengthens the evidence for the existence of these compounds in the amino-form. The broad absorption region between 2900 and 1500 cm.$^{-1}$ in adenine is absent from the spectrum of 9-methyladenine and is most probably due to the $N_{(9)}$–H vibration. A similar set of bands for purine between 2540 and 2750 cm.$^{-1}$ is removed on methylation at position 9. For nucleotides the spectra in the 3000 cm.$^{-1}$ region are not very satisfactory and hence no evidence could be obtained for or against zwitterion formation. However, for the hydrochlorides of adenine, cytosine, and guanine the main bands are broader but still in approximately the same position as those of the parent bases, again indicating that the proton is added to a ring-nitrogen atom and does not form an NH_3^+ group.

Guanine Derivatives.—Guanine (2-amino-6-hydroxypurine or a tautomeric form) bears a close structural relation to cytosine, except for the reversal of the positions of the amino- and hydroxyl-groups. It would, therefore, be expected that it exists in the same tautomeric form, *i.e.*, as the amino-keto-derivative; the infrared spectra can be satisfactorily interpreted along these lines. However, there are two important differences between guanine and cytosine which might show in the spectra of guanine derivatives. The first is that in the nucleosides the sugar units are attached to the $N_{(9)}$ atom and not to the pyrimidine ring. The second is that, according to the *X*-ray evidence on guanine hydrochloride,[16] the proton is added to the $N_{(7)}$ atom and hence the effect on the pyrimidine ring structure would be considerably less if analogous zwitterion formation occurs in guanylic acid.

The spectrum of guanine has two strong bands, at 1701 and 1681 cm.$^{-1}$, which are assigned to the C=O stretching and NH_2 deformation vibrations, respectively. The considerable shift of these bands to about 1735 and 1635 cm.$^{-1}$ in the spectra of guanosine and deoxyguanosine is difficult to explain, but may be due to differences in intermolecular hydrogen bonding between guanine and its nucleosides. In the case of deuterioguanine the band at 1695 cm.$^{-1}$ is ascribed to the C=O stretching vibration; the appearance of a new strong band at 1616 cm.$^{-1}$ closely parallels the case of deuteriocytosine.

The removal of one of the bands near 1600 cm.$^{-1}$ in guanine on deuteration supports the assignment of the NH_2 deformation vibration to this region. In the spectrum of deuterioguanosine the strong doublet at 1704 and 1680 cm.$^{-1}$ is assigned to the C=O vibration and resembles the spectrum of 6-hydroxy-2-methylpurine;[2] the reason for this doubling, however, is not clear in either case.

[16] Broomhead, *Acta Cryst.*, 1951, **4**, 81.

XUM

The lower-frequency band of the doublet at 1567 and 1555 cm.$^{-1}$ in guanine is assigned to the N–H deformation; it is removed on deuteration while the other band stays (at 1565 cm.$^{-1}$). This band persists for the other derivatives and is also given by the two acetyldeoxyguanosine derivatives, at 1545 and 1538 cm.$^{-1}$ severally. As mentioned previously, the addition of the sugar residue to guanine does not affect the hydrogen atom on $N_{(1)}$ and, therefore, the band at about 1540 cm.$^{-1}$ is expected to persist through the complete series, in agreement with experiment. Bands of considerable intensity in the spectrum of guanine at 1477 and 1375 cm.$^{-1}$ can be found in the spectra of all the other guanine derivatives in the same regions and are assigned to vibrations of the ring systems. The only other band common to the spectra of all the guanine derivatives (and the two acetyldeoxyguanosines) is the strong band at 785—775 cm.$^{-1}$. This is most probably due to the out-of-plane vibration of the only hydrogen atom attached to a carbon atom (at position 8). The strong band at 1698 cm.$^{-1}$ in guanylic acid is undoubtedly due to the C=O stretching vibration. The next band at 1608 cm.$^{-1}$ has a considerably lower frequency than the corresponding bands in the spectra of guanosine and deoxyguanosine. In the 3000 cm.$^{-1}$ region the spectrum of deuterioguanosine shows that deuteration in this case was not very satisfactory. However, the positions of the bands in guanine and the two nucleosides, and their shifts on deuteration, confirm the amino-structure for these compounds.

Sugar and Phosphate Groups.—All the nucleosides and nucleotides, and the corresponding deoxy-compounds examined, exhibited a number of strong bands in the region 900—1200 cm.$^{-1}$ which were not present in the spectra of the corresponding parent bases. A search was made for characteristic vibration frequencies of the ribose and deoxyribose units, but a careful examination of the spectra of all the sugar derivatives in the present work (20 ribose and 19 deoxyribose derivatives) has shown that no regularities could be found among the bands in this region. Ten such pairs of compounds were available for comparison. Barker *et al.*[17] found for sugar pyranosides that all the deoxy-compounds exhibited an additional band at 867 cm.$^{-1}$, which they have assigned to a CH_2 rocking mode. No such additional bands for the deoxy-derivatives could be found in the present series of compounds, although it should be realised that the spectra are more complex. An examination of the region 950—1200 cm.$^{-1}$, where the bands are due to C–O and C–C vibrations, showed that nearly all of these compounds gave five bands in this region. A statistical analysis of the frequencies of these bands indicated that only for one of these bands is there a significant difference in frequency (ribose 1076 $\pm$ 6·6 cm.$^{-1}$, deoxyribose 1087 $\pm$ 8·7 cm.$^{-1}$).

Fraser[18] has suggested that in the spectra of ribose nucleic acid and deoxyribose nucleic acid the bands at about 1087 cm.$^{-1}$ are due to the sugar ring and those at 1070 and 1052 cm.$^{-1}$, respectively, due to the phosphate group. Our results show that this assignment cannot be applied to the smaller units because a band at this position is given by 36 out of the 39 compounds examined and only 13 of these contain a phosphate group.

The spectra of the available nucleoside phosphates were carefully examined for any additional bands beyond those in the spectra of the corresponding nucleosides in the regions 1300—1200 (P=O band), and 1150—900 cm.$^{-1}$ (phosphate ion or P–O–C band), but none of these investigations yielded any bands characteristic of the phosphate grouping. It had, therefore, to be concluded that, because of the large number of strong bands already present in the spectra of the nucleosides, no characteristic bands of the phosphate group could be picked out in the spectra of the nucleoside phosphates. Tsuboi[19] has shown that a band in the region 1220—1240 cm.$^{-1}$ in the spectra of the sodium salts of nucleic acids can be assigned to a vibration of the PO_2^- group. He also ascribes bands at 980 and 1100 cm.$^{-1}$ in the spectra of nucleotides in aqueous solutions at high pH's to

[17] Barker and Stephens, *J.*, 1954, 4550.
[18] Fraser, " Progress in Biophysics," 1953, Vol. III, p. 47.
[19] Tsuboi, *J. Amer. Chem. Soc.*, 1957, **79**, 1351.

XUM

vibrations of the PO_3^{2-} group, but observes that these bands disappear at lower pH's. This absence of bands is consistent with our findings on the solid nucleotides where the phosphate group presumably exists as PO_3H_2, or as PO_3H^- when zwitterion formation has occurred.

The important problem of the position of the phosphate group on the sugar entity in the case of the *a* and *b* isomers of the nucleotides was also studied by the examination of the 950—1100 cm.$^{-1}$ region in the spectra of the three pairs of isomers (the adenylic acids, the cytidylic acids, and the cytidine benzyl phosphates). It was found that in each case the *a* isomers gave only one strong band (at 1059, 1069, and 1075 cm.$^{-1}$, respectively), while the *b* isomers gave two strong bands (at 1042, 1070; 1042, 1075, and at 1047, 1074 cm.$^{-1}$, respectively). The guanylic and uridylic acids, which were only available as the *b* isomers, also gave two pairs of strong bands (1057, 1078; and 1042, 1075 cm.$^{-1}$, respectively) in this region. However, the spectra of a larger number of isomeric pairs will have to be examined to find out whether this correlation is of general applicability.

Cytidine, uridine, adenosine, and thymidine were also examined in neutral water and deuterium oxide solutions. By comparing these spectra with those of the same compounds in the solid state, it was found that only the stronger bands appeared in the solution spectra but that every band corresponded exactly to a band in the solid state spectrum, within the experimental error. These observations, that the spectra do not change when the compounds are dissolved in water, are of importance when attempts are made to extend the results for the simple compounds obtained in the solid state to the spectra of the nucleic acids of high molecular weight that are always examined in a highly hydrated state.

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101. *Diaryls. Part III.*[1,2] *Reactions of Some Dihalogenonaphthalenes with Lithium Amalgam, and Simple Syntheses of* 2,3:6,7-*Dibenzobiphenylene.*

By E. R. Ward and B. D. Pearson.

The reactions of some *o*-dihalogenonaphthalenes with lithium amalgam in ether or tetrahydrofuran have been studied. 2,3-Dibromonaphthalene yields 2,3:6,7-dibenzobiphenylene, which thus becomes readily accessible. The dibenzobiphenylene is also simply obtained by refluxing 2-bromo-3-iodonaphthalene with copper bronze in dimethylformamide, this being a completely new type of synthesis for aromatic derivatives of cyclobutadiene.

2,3:6,7-Dibenzobiphenylene was synthesised by Ward and Pearson [1] and by Curtis and Viswanath,[3] by methods involving at least ten stages from 1,2,3,4-tetrahydronaphthalene. We have now obtained it, in low yield, in two stages from the commercially available 2,3-diaminonaphthalene.[4] The latter is converted into 2,3-dibromonaphthalene by a

[1] Part I, Ward and Pearson, *J.*, 1959, 1676.
[2] Part II, Ward and Pearson, *J.*, 1959, 3378.
[3] Curtis and Viswanath, *J.*, 1959, 1670.
[4] Pearson, *Chem. and Ind.*, 1960, 899.

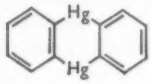
XUM

Sandmeyer reaction and then treated with lithium amalgam in ether. 2,3:6,7-Dibenzobiphenylene is presumably formed by way of a β-naphthalyne intermediate.

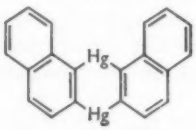
Wittig and Pohmer [5] found that *o*-bromofluorobenzene reacted with lithium amalgam in ether to give 24% of biphenylene, 3% of triphenylene, and 2% of the 9,10-dimercuraanthracene (I), whereas *o*-dibromobenzene gave 9% of biphenylene and 42% of the mercurial; formation of biphenylene was ascribed to the dimerisation of a benzyne intermediate. Following their procedure we have now treated lithium amalgam (prepared in a Schlenk tube) with solutions of *o*-dihalogenonaphthalenes in ether (E) or tetrahydrofuran (T) for 24 hr. The products were separated, as far as possible, by fractional crystallisation, vacuum-sublimation, or vacuum-distillation, with results as tabulated.

Compound	Products
1,2-Dibromonaphthalene (E)	Mercury compound, (II)
,, ,, (T)	2,2′-Binaphthyl
1-Bromo-2-fluoronaphthalene (E)	(II) and a polymer (?)
,, ,, (T)	2-Fluoronaphthalene
2,3-Dibromonaphthalene	2,3:6,7-Dibenzobiphenylene
6-Bromo-7-fluoro-1,2,3,4-tetrahydronaphthalene failed to react.	

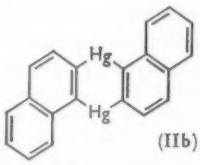
The mercury compound (II), by analogy with (I), may be formulated as (IIa or b). Since 1,2-dibromonaphthalene gives 2,2′-binaphthyl when the reaction is carried out in



(I)



(IIa)



(IIb)

tetrahydrofuran it seems possible that 1,2:7,8-dibenzobiphenylene could have been formed initially, decomposing to the binaphthyl, a known reduction product.[6] The molecular weight (590) suggests that the supposed polymer is $(C_{10}H_6F)_4$ (*M*, 580).

A new method of synthesising aromatic derivatives of cyclobutadiene was discovered when we found that refluxing 2-bromo-3-iodonaphthalene with copper bronze in dimethylformamide gave 2,3:6,7-dibenzobiphenylene in low yield. This reaction also probably proceeds through a β-naphthalyne intermediate; the latter may be stabilised in this case by solvation with the highly polar solvent. Since a similar reaction with *o*-bromoiodobenzene yielded only biphenyl, the success recorded above may be due to the exceptional stability of 2,3:6,7-dibenzobiphenylene.[4]

In the preparation of 1,2-dibromonaphthalene it was found that rapid addition of diazotised 1-bromo-2-naphthylamine to the Sandmeyer reagent gave 1,1′-dibromo-2,2′-azonaphthalene as a by-product, confirming the work of Bogoslovskii and Kozakova.[7]

Experimental

1,2-Dibromonaphthalene.—1-Bromo-2-naphthylamine (10 g.) was diazotised as previously described [1] and the filtered solution added rapidly to the stirred solution of cuprous bromide (20 g.) in 48% w/w hydrobromic acid (200 ml.). After 4 hr. the mixture was poured into ice-water (2 l.) and the brown solid collected (12 g.; 90%, m. p. 58°). Crystallisation of this from benzene gave 1,1′-dibromo-2,2′-azonaphthalene (0·5 g.), m. p. 266° (Bogoslovskii and Kozakova [7] give 252°) (Found: C, 55·4; H, 2·9; N, 6·3; Br, 35·4. Calc. for $C_{20}H_{12}Br_2N_2$: C, 54·5; H, 2·7; N, 6·4; Br, 36·4%). Further concentration of the benzene gave pure 1,2-dibromonaphthalene, m. p. 68° (lit.,[8] 68°), whose *complex* with 2,4,7-trinitrofluorenone had m. p. 163° (from benzene) (Found: C, 46·6; H, 1·9; N, 7·4; Br, 26·5. $C_{23}H_{11}Br_2N_3O_7$ requires C, 45·8; H, 1·8; N, 7·0; Br, 26·6%).

[5] Wittig and Pohmer, *Ber.*, 1956, **89**, 1334.
[6] Cava and Stucker, *J. Amer. Chem. Soc.*, 1955, **77**, 6022.
[7] Bogoslovskii and Kozakova, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1183.
[8] Meldola and Streatfield, *J.*, 1893, **63**, 1054.

1-*Bromo*-2-*fluoronaphthalene*.—1-Bromo-2-naphthylamine (30 g.) was dissolved in hydrochloric acid (*d* 1·2; 34 ml.) and water (34 ml.) and diazotised by sodium nitrite (12 g.) in water (30 ml.) at 0°, and the filtered diazo-solution added to 40% fluoroboric acid (50 ml.). After 3 hr. the diazonium fluoroborate was collected, washed with ice-water (50 ml.), and air-dried (34 g., 78%). It was then heated at 145° for 1 hr. The resultant tar was extracted with boiling benzene (2 × 100 ml.), and the extract filtered through alumina (2 × 20 cm.) and evaporated, giving a yellow solid (17 g.; m. p. 62°). Vacuum-distillation gave 1-bromo-2-fluoronaphthalene (15 g., 63%), b. p. 90—92°/2 mm., m. p. 68° (from methanol–water, 5 : 1 v/v) (Nakata [9] gives 49°) (Found: C, 54·0; H, 3·1; Br, 34·4. Calc. for $C_{10}H_6BrF$: C, 53·3; H, 2·7; Br, 35·4%).

2-*Bromo*-1-*fluoronaphthalene*, obtained similarly (75%) from 2-bromo-1-naphthylamine, had b. p. 164°/2 mm., n_D^{25} 1·648 (Found: C, 53·9; H, 2·8%).

6-*Amino*-7-*bromo*-1,2,3,4-*tetrahydronaphthalene*.—6-Bromo-1,2,3,4-tetrahydro-7-nitronaphthalene (12 g.) was refluxed with iron powder (300-mesh; 120 g.), ferrous ammonium sulphate (6 g.), and water (600 ml.) for 4 hr. Steam-distillation gave 6-amino-7-bromo-1,2,3,4-tetrahydronaphthalene (6·6 g., 62%), m. p. 46—47° [from light petroleum (b. p. 80—100°)] (Found: C, 54·0; H, 5·5; Br, 34·5. Calc. for $C_{10}H_{12}BrN$: C, 53·1; H, 5·3; Br, 35·4%).

6-*Bromo*-7-*fluoro*-1,2,3,4-*tetrahydronaphthalene*.—Proceeding as for 1-bromo-2-fluoronaphthalene gave a 65% yield of diazonium fluoroborate, decomposition of which followed by vacuum-distillation gave 6-bromo-7-fluoro-1,2,3,4-tetrahydronaphthalene (2·6 g., 60%), b. p. 126°/4 mm., n_D^{25} 1·70 (Found: C, 53·7; H, 4·6. Calc. for $C_{10}H_{10}BrF$: C, 52·4; H, 4·4%).

Reaction of Lithium Amalgam with o-*Dihalogenonaphthalenes*.—(a) *General procedure*. Lithium (0·3 g.) was weighed in an atmosphere of oxygen-free hydrogen (all operations being carried out under this gas) and added portionwise to mercury (100 g.; previously heated to 180°) in a Schlenk tube. Then the temperature was raised to 210° for 30 min.; when cool, the apparatus was transferred to a dry box, and the solution (15 ml.; but for 2,3-dibromonaphthalene 75 ml.) of the halogeno-compound (15 millimoles) was added. The Schlenk tube was shaken, horizontally, for 24 hr., then washed out with solvent, the mercury was separated from solvent and other solids, and the solids (A) were collected, washed with water to remove lithium salts, and dried. From the residual solvent a tar (B) was obtained by evaporation.

(b) 1,2-*Dibromonaphthalene in ether*. Extraction of the solids (A) with boiling dimethylformamide (50 ml.) left a grey residue (0·8 g.), m. p. 360° (Found: C, 11·8; H, 0·84%). Concentration of the extract gave the *dimercura-anthracene* as a white amorphous powder (2·35 g.), m. p. 323—325° (Found: C, 36·8; H, 1·8. $C_{20}H_{12}Hg_2$ requires C, 36·7; H, 1·5%). Attempts to obtain products from the tar (B) failed.

(c) 1,2-*Dibromonaphthalene in tetrahydrofuran*. The buff-grey material (A) (0·7 g.), m. p. 360° (Found: C, 22·7; H, 3·5%), was insoluble in boiling dimethylformamide. Chromatography of the tar (B) in benzene on alumina gave two bands; the first was eluted with benzene giving an orange tar (0·6 g.), which, from ethanol, gave pure 2,2′-binaphthyl (identified by mixed m. p.).

(d) 1-*Bromo*-2-*fluoronaphthalene in ether*. Boiling dimethylformamide (50 ml.) was used to extract the solid (A), leaving a grey mercury-contaminated residue. Concentration of the extract gave a product, supposedly (II) (0·9 g.), m. p. 323°. The tar (B) was dissolved in dimethylformamide (15 ml.); adding this solution to water gave a buff solid *polymer* (1·6 g.), m. p. 256—258° [Found: C, 83·0; H, 4·2%; *M*, 590. $(C_{10}H_6F)_4$ requires C, 82·8; H, 4·2%; *M*, 580]. This sublimed at 4 mm.; it did not form a complex with 2,4,7-trinitrofluorenone.

(e) 1-*Bromo*-2-*fluoronaphthalene in tetrahydrofuran*. The grey solids (A) (0·15 g.), m. p. 360°, were insoluble in dimethylformamide. Chromatography of the tar (B) on alumina in benzene gave two bands; the first, eluted with benzene, gave 2-fluoronaphthalene (1·0 g., 45%), m. p. 58° [from light petroleum (b. p. 80—100°)] (picrate, m. p. 100°) (Schiemann *et al.*[10] give m. p. 60° and 100° respectively); the second band afforded only a tar (0·2 g.).

(f) 2,3-*Dibromonaphthalene in ether*. Extraction of material (A) by boiling dimethylformamide (50 ml.) gave a mercury-contaminated residue but concentration of the extract afforded a buff solid (1·4 g.), m. p. 263° (Found: C, 60·8; H, 4·0; Br, 6·5%). Chromatography of the tar (B) on alumina in benzene gave two bands; the first, by elution with benzene, gave 2,3:6,7-dibenzobiphenylene (7 mg. identified by its ultraviolet spectrum, m. p., and trinitrofluorenone complex) and a brown tar (0·1 g.). The second, eluted by benzene–ethyl acetate (4 : 1 v/v) gave a tar (0·2 g.), which on extraction with warm ethanol (10 ml.) left an amorphous

[9] Nakata, *Ber.*, 1931, **64**, 2059.
[10] Schiemann, Gueffroy, and Winkelmuller, *Annalen*, 1931, **487**, 270.

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brown powder (0·2 g.), m. p. 238° (Found: C, 72·6; H, 4·7; Br, 10·0%; *M*, 692), which did not crystallise or sublime.

Reaction of 2-Bromo-3-iodonaphthalene with Copper Bronze in Dimethylformamide.—2-Bromo-3-iodonaphthalene (2·5 g.) was refluxed with copper bronze (4 g.) in dimethylformamide (25 ml.) for 3 hr. The solids were then removed and the hot filtrate was poured into water (250 ml.). The next day the sticky solids that separated were collected, dissolved in benzene, and filtered through alumina (2 × 20 cm.). Concentration gave 2,3:6,7-dibenzobiphenylene (identified as above) (8 mg., 0·9%), and further concentration a tar (1·3 g.). Steam-distillation of the tar gave 2-bromonaphthalene (0·3 g., 19%) and left an uncrystallisable residue.

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102. 1,2,4-*Triazoles. Part II.*[1] 3-*Alkyl*-5-*aryl*-1,2,4-*triazoles.**

By D. R. LILJEGREN and K. T. POTTS.

Several triazoles of the above type have been synthesised by the fusion of aromatic cyanides with hydrazide benzenesulphonates of aliphatic acids. Diaryltriazoles are also formed, mainly when acethydrazide benzenesulphonate is used, and evidence is presented to account for these products. This synthesis is restricted to the use of aromatic cyanides and hydrazide benzenesulphonates of aliphatic or aromatic acids.

IN a previous communication[1] the fusion of a benzene-, *p*-nitrobenzene-, or toluene-*p*-sulphonic acid salt of an arylhydrazide with an aromatic cyanide was shown to yield a 3,5-diaryl-1,2,4-triazole. This paper describes the preparation of 3-alkyl-5-aryl-1,2,4-triazoles * from aromatic cyanides and hydrazide benzenesulphonates of aliphatic acids, and shows that the method is not satisfactory for the preparation of 3,5-dialkyl-1,2,4-triazoles.

The condensation is effected by heating together equimolar quantities of the reactants at 200° for 1—2 hours. A 3,5-diaryltriazole is sometimes found associated with the 3-alkyl-5-aryltriazole, with the aryl groups corresponding to that of the aromatic cyanide used. The diaryltriazole must be formed either by reaction of the aromatic cyanide with some intermediate product or by a similar condensation between products derived from the initial reactants in some way. Evidence suggests that triazole formation occurs through the intermediate hydrazidinium salt (I). This would immediately undergo ring closure with elimination of water,[2] rather than further reaction with unchanged cyanide. That the diaryltriazole is actually formed in a similar condensation was verified for the reaction of *o*-tolyl cyanide with hydrazide benzenesulphonates of aliphatic acids. From several of these reactions *o*-toluamide was isolated. This must arise by hydration of the *o*-tolyl cyanide, the necessary water coming from the ring closure that occurs simultaneously. Under these reaction conditions cyanides are known[3] to give amides very readily. The amide formed is then available to take part in a transamination: $R'\cdot CO\cdot NH_2 + R\cdot CO\cdot NH\cdot NH_2 \rightleftharpoons R'\cdot CO\cdot NH\cdot NH_2 + R\cdot CO\cdot NH_2$. Similar transaminations under related

* As the position of the imino-hydrogen is unknown, these may also be regarded as 5-alkyl-3-aryl-1,2,4-triazoles.

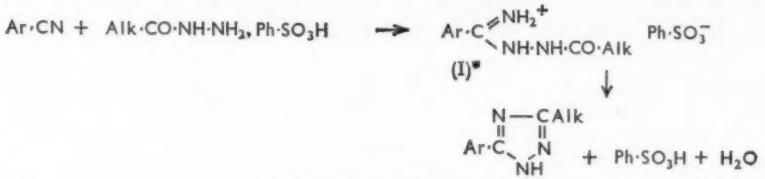
[1] Part I, Potts, *J.*, 1954, 3461.

[2] (*a*) Atkinson and Polya, *J.*, 1954, 3323; (*b*) Atkinson and Polya, *J. Amer. Chem. Soc.*, 1953, **75**, 1471; (*c*) Pinner, *Ber.*, 1894, **27**, 997.

[3] Kilpatrick, *J. Amer. Chem. Soc.*, 1947, **69**, 42; DeBenneville, Levesque, Exner, and Hertz, *J. Org. Chem.*, 1956, **21**, 1072.

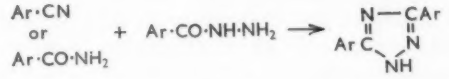
XUM

conditions have been noted previously,[4,5] and recent investigations have shown [6] that at temperatures of 180—200° the equilibrium in the fusion of an aliphatic amide, particularly a substituted acetamide, and an amine salt is shifted completely to the right in 15 min. In the Pellizzari synthesis involving fusion of an amide and a hydrazide at 200—280°,



* Or an equivalent formulation.

mixtures of triazoles are nearly always obtained, particularly when acethydrazide is used; [4] *e.g.*, from benzamide and acethydrazide a mixture of 3,5-diphenyl-, and 3-methyl-5-phenyl-1,2,4-triazole is obtained; [2a] this side reaction is the main disadvantage of the Pellizzari method.[7] It has now been shown that in the fusion of benzamide and acethydrazide benzenesulphonate the equilibrium in the initial transamination is shifted completely to the right, so that only 3,5-diphenyl-1,2,4-triazole is isolated from the reaction. These results suggest that after formation in the transamination the arylhydrazide can condense in two ways, the over-all result being the same. The first involves reaction with unchanged cyanide,[1] and the second a Pellizzari-type reaction with the aromatic amide. As all these species are present in the melt at the same time the two reactions probably occur concurrently.



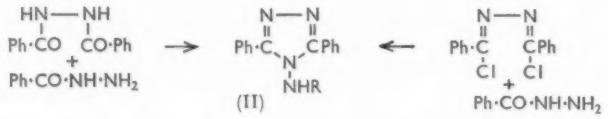
In agreement with earlier observations [4] it was found that propionhydrazide only underwent transamination to a small extent, and butyrhydrazide appeared not to react at all.

Attempts to prepare these triazoles by the alternative route, the fusion of alkyl cyanides with the hydrazide benzenesulphonate of an aromatic acid, were unsuccessful. From the attempted condensation of methyl cyanide or ethyl cyanide with benzhydrazide benzenesulphonate at 200° the same compound was isolated, and shown to be 4-benzamido-3,5-diphenyl-1,2,4-triazole (II; R = Bz). This can only result by self-condensation of benzhydrazide in some way. It is known that fusion of benzhydrazide [8,9] or its benzenesulphonate at 260° readily yields 4-amino-3,5-diphenyl-1,2,4-triazole (II; R = H); and, when benzhydrazide is heated under reflux for short periods with a small amount of benzenesulphonic acid in an ionising solvent such as dimethylformamide, dibenzoylhydrazine is one of the products formed. This suggests that in the above reaction the alkyl cyanide merely acts as an ionising solvent and the intermediate dibenzoylhydrazine condenses with unchanged benzhydrazide to form the triazole (II; R = Bz). This compound has previously been obtained in a related reaction by condensation of benzhydrazide and di-(α-chlorobenzylidene)hydrazine.[10] Methyl cyanide with aniline hydrochloride forms a mixture of *N*-phenyl- and *NN*-diphenyl-acetamidine [11] and on enhancement of its

[4] Pellizzari, *Gazzetta*, 1911, **41**, 20.
[5] Hoggarth, *J.*, 1949, 1164.
[6] Gerchuk, Lifshits, and Taits, *J. Gen. Chem.* (*U.S.S.R.*), 1950, **20**, 924; Ridel and Gerchuk, *ibid.*, 1958, **28**, 1365.
[7] Potts, *Chem. Rev.*, 1960, in the press.
[8] Stolle, *J. prakt. Chem.*, 1903, **68**, 464.
[9] Silberrad, *J.*, 1900, **77**, 1190.
[10] Stolle and Thomä, *J. prakt. Chem.*, 1906, **73**, 295.
[11] Bernthsen, *Annalen*, 1877, **184**, 290.

XUM

activity by combination with a catalyst such as aluminium chloride [12] it reacts with aniline itself, forming the same amidines. In trichloromethyl cyanide [13] the inductive effect of the polar substituents so increases the positive character of the α-carbon atom that amidine formation occurs very readily. Indeed, with nitromethyl cyanide, salts and not amidines are formed.[14] Thus it appears that benzenesulphonic acid is not a sufficiently strongly cationoid catalyst to effect the condensation of an alkyl cyanide and a hydrazide.



Reaction of methyl cyanide with acethydrazide benzenesulphonate also did not give the expected triazole. No homogeneous product, apart from hydrazine dibenzenesulphonate, which is probably formed in the working up of the reaction mixture, was isolated.

The opportunity is taken to record some incidental observations. Heating an equimolar mixture of cyanide, hydrazide, and benzenesulphonic acid affords the triazole in yields similar to those obtained when the benzenesulphonate salt is used. No increase in yield occurs from reaction in sealed tubes. Methyl cyanide does not react with the hydrazide benzenesulphonate under these conditions. Replacement of the hydrazide salt with an acylarylhydrazine salt should give rise to a 1,3,5-trisubstituted 1,2,4-triazole. However, benzenesulphonate salts of these substituted hydrazides could not be obtained; in all the instances investigated the acyl group was either eliminated and the benzenesulphonate salt of the arylhydrazine obtained or the material was recovered unchanged. The alternative method, heating of the three components together, was not successful, no identifiable products being isolated.

Experimental

Evaporation of solvents was under reduced pressure on a water-bath. Light petroleum refers to the fraction of b. p. 60—80°.

Hydrazide Benzenesulphonates.—General method. The hydrazide, dissolved in the minimum amount of warm ethanol, was treated with a 10% excess of benzenesulphonic acid, added in small portions, with occasional cooling. The salt was precipitated by the addition of an equal volume of dry ether, collected, and dried (yield usually >90%). *Acethydrazide benzenesulphonate* crystallised from ethanol–ether as needles, m. p. 175—176° (Found: C, 41·4; H, 4·9. $C_8H_{12}N_2O_4S$ requires C, 41·4; H, 5·2%), and *propionhydrazide benzenesulphonate* as plates, m. p. 149—150° (Found: C, 43·8; H, 5·6. $C_9H_{14}N_2O_4S$ requires C, 43·9; H, 5·7%). *Butyrhydrazide benzenesulphonate* crystallised as needles, m. p. 161—162°, from ethanol (Found: C, 46·4; H, 6·2. $C_{10}H_{16}N_2O_4S$ requires C, 46·2; H, 6·2%). In the preparation of those salts, particularly benzhydrazide benzenesulphonate, where boiling alcohol is required to effect dissolution of the hydrazide, a small quantity of a white, insoluble product soon appears after addition of the benzenesulphonic acid. This was identified as hydrazine dibenzenesulphonate by direct comparison (m. p., infrared and ultraviolet spectra) with a specimen prepared from hydrazine and two mols. of benzenesulphonic acid. It crystallised from a large volume of ethanol as plates, m. p. 284—285° (decomp.) [15] (*vacuo*) (Found: C, 41·8; H, 4·7; N, 8·0; S, 18·4. Calc. for $C_{12}H_{16}N_2O_6S_2$: C, 41·4; H, 4·6; N, 8·0; S, 18·4%).

3-Alkyl-5-aryl-1,2,4-triazoles.—General method. The hydrazide benzenesulphonate (0·05 mole) and the aromatic cyanide (0·05 mole) were heated together in a vapour-bath at 200° for

[12] Oxley, Partridge, and Short, *J.*, 1947, 1110.
[13] G.P. 671,785; *Chem. Abs.*, 1939, **33**, 6345; Oxley, Partridge, and Short, *J.*, 1948, **303**; Grivas and Taurins, *Canad. J. Chem.*, 1958, **36**, 771.
[14] Grivas and Taurins, *Canad. J. Chem.*, 1959, **37**, 1266.
[15] Curtius and Lorenzen, *J. prakt. Chem.*, 1903, **58**, 177.

1—2 hr. Effervescence usually occurred for about 45 min. and water formed on the walls of the tube. An equal volume of water was added to the cooled melt and the solution brought to pH ~7 with sodium hydroxide or carbonate. Any solid that separated (usually only 3,5-diphenyltriazole) was removed and the solution extracted with ether. After working up of the ether extract in the usual way, the partly crystalline residue was purified by one of two methods. In condensations involving the use of phenyl cyanide, the 3-alkyl-5-phenyltriazole was extracted from the more insoluble 3,5-diphenyltriazole with light petroleum. Purification was then by recrystallisation or by distillation followed by recrystallisation. With *o*-tolyl cyanide purification was slightly more difficult owing to the presence of a three-component mixture. The crude material was separated into two fractions by distillation *in vacuo*. The low-boiling fraction was mainly *o*-toluamide, contaminated with the 3-alkyl-5-*o*-tolyltriazole which was removed by extraction with light petroleum. After several recrystallisations from benzene, the *o*-toluamide separated as needles, m. p. 140—141° alone or on admixture with an authentic specimen that had an identical infrared spectrum (Found: C, 71·4; H, 6·7. Calc. for C_8H_9NO: C, 71·1; H, 6·7%). The high-boiling fraction was purified by recrystallisation or, if this was insufficient, by chromatography in benzene on neutral alumina (activity 1). A small amount of *o*-toluamide was eluted first. The 3-alkyl-5-*o*-tolyltriazole was recrystallised or further purified by sublimation *in vacuo*. From the recrystallisation mother-liquors a small amount of 3,5-di-*o*-tolyltriazole was isolated as the picrate.

The *products* obtained are recorded in the Table.

Triazoles prepared by the reaction of aromatic cyanides with hydrazide benzenesulphonates of aliphatic acids.

Substituents		M. p.	Crystn. solvent[f]	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Me	Ph	166°[2a]	C_6H_6	25	67·9	5·4	—	$C_9H_9N_3$	67·9	5·7	—
Et	Ph	103—104	,,	18	69·4	6·3	24·0	$C_{10}H_{11}N_3$	69·3	6·4	24·3
Pr	Ph	71—72	Aq. EtOH	31	67·3	7·3	21·0	$C_{11}H_{13}N_3,0·5H_2O$[g]	67·4	7·1	21·4
Me	*o*-Tolyl	140—141	C_6H_6–Pet	50	69·6	6·4	23·9	$C_{10}H_{11}N_3$	69·3	6·4	24·3
Et	,,	87	,,	50	70·6	6·9	22·5	$C_{11}H_{13}N_3$[e]	70·6	7·0	22·5
Pr	,,	124—126	C_6H_6	40	72·0	7·6	20·8	$C_{12}H_{15}N_3$	71·6	7·5	20·9
Et	CH_2Ph	230—240/ 0·1 mm.[b]	—	—	70·1	6·9	—	$C_{11}H_{13}N_3$	70·6	7·0	—
Ph	Ph	189—190[1]	Pet	14	—	—	—	$C_{14}H_{11}N_3$	—	—	—
o-Tolyl	*o*-Tolyl	190—191	EtOH	—	55·3	3·9	17·4	$C_{22}H_{20}N_6O_7$[d]	55·0	4·2	17·5

[a] *Picrate*, prisms (from benzene), m. p. 129—130° (Found: C, 49·2; H, 3·9; N, 20·1. $C_{17}H_{16}N_6O_7$ requires C, 49·1; H, 3·9; N, 20·2%). [b] B. p. [c] Identity established by comparison of infrared spectrum with that of authentic specimen. [d] Isolated as picrate containing $1H_2O$. [e] *Picrate*, needles (from benzene), m. p. 138° (Found: C, 52·1; H, 4·1; N, 19·0. $C_{17}H_{16}N_6O_7,0·3C_6H_6$ requires C, 51·6; H, 4·1; N, 19·0%). Pet = light petroleum.

Attempted Condensation of Methyl Cyanide with Benzhydrazide Benzenesulphonate.—*4-Benzamido-3,5-diphenyl-1,2,4-triazole.* A mixture of methyl cyanide (1·6 g., 0·04 mole) and benzhydrazide benzenesulphonate (12·9 g., 0·044 mole) was heated under reflux at 200° for 2 hr., benzhydrazide subliming. The cooled melt was dissolved in sodium hydroxide solution, treated with charcoal, and acidified with concentrated hydrochloric acid. The sticky, grey precipitate crystallised, and separated from ethanol as prisms, m. p. 244—245° (lit.,[10] m. p. 240°) (Found: C, 74·2; H, 4·7; N, 16·6. Calc. for $C_{21}H_{16}N_4O$: C, 74·1; H, 4·7; N, 16·5%).

4-Amino-3,5-diphenyl-1,2,4-triazole.—Benzhydrazide benzenesulphonate (8·8 g., 0·03 mole) was heated at 200° for 2 hr. Water was evolved and a small amount of benzhydrazide sublimed. 4-Amino-3,5-diphenyl-1,2,4-triazole (1·1 g., 32%) was isolated by chloroform-extraction of the cooled melt rendered alkaline with sodium hydroxide solution. It crystallised from ethanol as plates, m. p. 259—260° (lit.,[8,16] m. p. 263°, 258°), and formed a picrate, plates (from benzene), m. p. 156—157° (lit.,[16] m. p. 154°).

Fusion of Acethydrazide Benzenesulphonate and Benzamide.—Acethydrazide benzenesulphonate (1·2 g., 0·005 mole) and benzamide (0·6 g., 0·005 mole) were heated together at 200° for 2 hr. A small amount of benzhydrazide sublimed. Water (10 ml.) was added to the cooled melt, this solution neutralised with sodium carbonate, and by ether-extraction and working up in the usual way an oil was obtained that crystallised slowly. After crystallisation from ethanol and then light petroleum (b. p. 60—80°) needles of 3,5-diphenyl-1,2,4-triazole, m. p.

[16] Franzen and Kraft, *J. prakt. Chem.*, 1911, **84**, 129.

187°, were obtained. The m. p. was not depressed on admixture with an authentic specimen whose infrared spectrum was identical with that of the above product.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, University of Melbourne. D. R. L. thanks the C.S.I.R.O. for the award of a junior postgraduate studentship.

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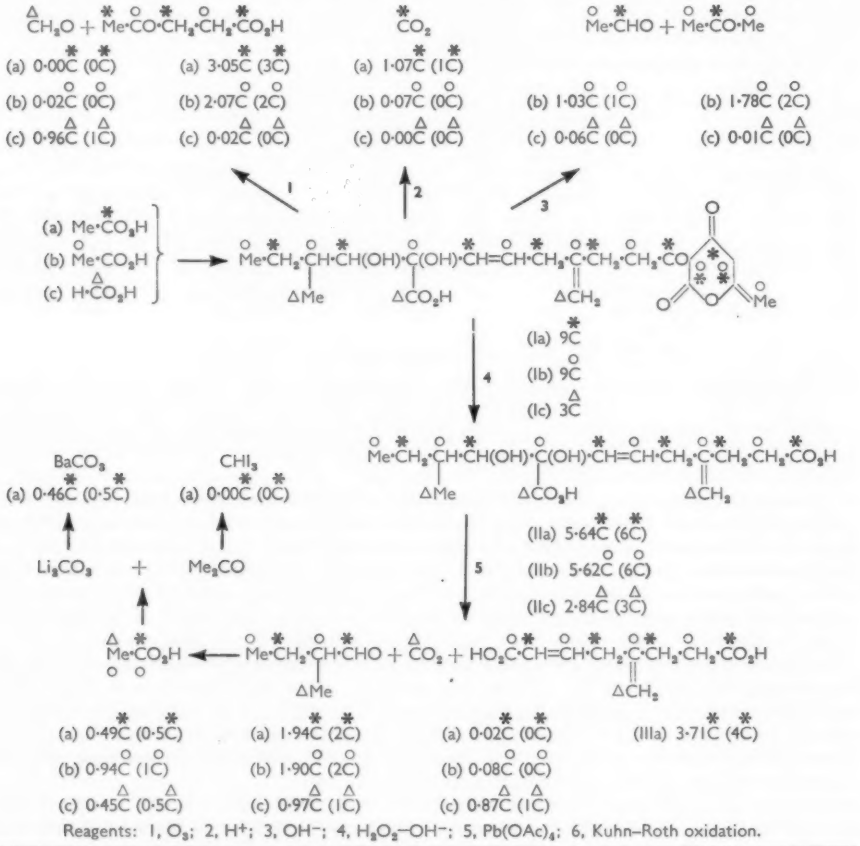
103. *Alternaric Acid. Part V.* Biosynthesis.*

By W. B. TURNER.

Alternaric acid is biosynthesised from nine acetate units and three C_1 units derivable from formate. Incorporation of propionate probably proceeds *via* acetate.

ALTERNARIC ACID [1,2] (I) is a natural product having a branched-chain not obviously derivable from mevalonate. Birch and his collaborators suggested [3] that many such



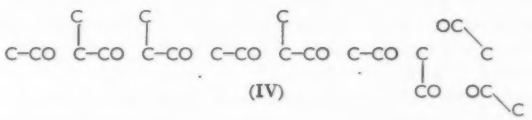
* Part IV, *J.*, 1960, **3413**.

[1] Bartels-Keith and Grove, *Proc. Chem. Soc.*, 1959, **398**.
[2] Bartels-Keith, *J.*, 1960, **1662**.
[3] Birch, Elliott, and Penfold, *Austral. J. Chem.*, 1954, **7**, 169; Birch, *Fortschr. Chem. org. Naturstoffe*, 1957, **14**, 186.

compounds may be formed by head-to-tail linkage of acetate units followed by the introduction of C_1 units and produced evidence [4] that this is the case for several natural products.

By this mode of biosynthesis, alternaric acid produced in the presence of [^{14}C]-labelled acetate and formate would possess the labelling pattern shown in (I). *Alternaria solani* has been grown on media containing, in separate experiments, Me·$^{14}CO_2H$, $^{14}CH_3$·CO_2H, and H·$^{14}CO_2H$ to give labelled alternaric acid. The incorporation of radioactivity (0·3, 0·3, and 0·2% respectively) was lower than is usual for this type of compound (cf., *e.g.*, ref. 4). The alternaric acid has been degraded by procedures described previously, as shown in the scheme, where the results of radioactivity assays are expressed according to methods used by Birch and his co-workers.[5] The results confirm the expected biogenesis. Agreement between the experimental and the theoretical values is not as close (3%) as might be expected; the deviation is not due to counting errors because (i) repetition of three of the degradations of compound (Ia) gave products whose count-rates differed from those shown in the scheme by only 1—2%, and (ii) there is agreement between the degradations of compounds (Ia and b).

That C_1 units are utilized in the formation of alternaric acid and similar compounds does not exclude the possibility of initial formation of C_3 units (*e.g.*, propionate) which might be incorporated during the chain-building process as shown (IV). It has been



(IV)

pointed out [6] that such a pathway would account for the branched-chain structures of the macrolides, and recent evidence [7] suggests that propionate is directly incorporated into erythromycin. When *A. solani* was grown on a medium containing Et·$^{14}CO_2H$ the radioactivity was incorporated into the alternaric acid to a very low degree (0·003%). Acid-hydrolysis of the alternaric acid produced gave the lactone-carbonyl atom as carbon dioxide which was counted as barium carbonate. The ratio of the relative molar activity of the alternaric acid to that of the barium carbonate was 9 : 0·78, providing a strong indication that the radioactivity has been incorporated after preliminary breakdown of the propionate to acetate.

When *A. solani* was grown in the presence of [2-^{14}C]-mevalonate the radioactivity was incorporated into the alternaric acid to such a low degree (0·001%) that no degradations were possible. The low incorporation of radioactivity, together with the results of the acetate fermentations, precludes the direct incorporation of mevalonate into alternaric acid.

Experimental

Assays of radioactivity were carried out by essentially standard methods.[5,8] Relative molar activities (r.m.a.) (a), (b), and (c) refer to labelled alternaric acid and its degradation products derived from Me·$^{14}CO_2H$, $^{14}CH_3$·CO_2H, and H·$^{14}CO_2H$ respectively.

[^{14}C]*Alternaric Acid.*—*Alternaria solani* (Ell. and Mart.) Jones and Grout (Strain 1342) was grown on a dextrose–nitrate medium, the labelled substrate (0·5—1 mc; *ca.* 0·125 mc per l. of culture medium) being added in aqueous solution at inoculation. After 15 days, the alternaric acid was isolated by chloroform-extraction of the acidified culture medium and was

[4] Birch, English, Massy-Westropp, Slaytor, and Smith, *J.*, 1958, 365; Birch, Fitton, Pride, Ryan, Smith, and Whalley, *ibid.*, p. 4576.
[5] Birch, Massy-Westropp, and Smith, *J.*, 1958, 360 and subsequent papers.
[6] Flynn, Gerzon, Monahan, Quarck, Sigal, Weaver, and Wiley, *Chem. Eng. News*, 1956, **34**, 5138; Woodward, *Angew. Chem.*, 1957, **69**, 50.
[7] Grisebach, Achenbach, and Grisebach, *Naturwiss.*, 1960, **47**, 206.
[8] Popjak, *Biochem. J.*, 1950, **46**, 560.

XUM

recrystallised from benzene and then from aqueous methanol to give the monohydrate, m. p. 135—139° [Found: r.m.a. × 10^{-3}, (a) 611·9; (b) 452·0; (c) 306·4].

Degradation of [^{14}C]*Alternaric Acid.*—(i) Hydrolysis with boiling N-sulphuric acid for 2½ hr. gave carbon dioxide isolated as barium carbonate [Found: r.m.a. × 10^{-3}, (a) 72·9 (1C, 68·0); (b) 3·9; (c) 1·6].

(ii) Hydrolysis with N-sodium hydroxide [2] gave acetaldehyde dimethone, m. p. 135—138° [Found: r.m.a. × 10^{-3}, (b) 51·6 (1C, 50·2); (c) 6·0], and acetone 2,4-dinitrophenylhydrazone, m. p. 123—126° [Found: r.m.a. × 10^{-3}, (b) 89·5 (2C, 100·4); (c) 1·5].

(iii) Ozonolysis in methyl acetate at −50° [9] gave formaldehyde dimethone, m. p. 191—192° [Found: r.m.a. × 10^{-3}, (a) 0·29; (b) 2·0; (c) 97·1 (1C, 102·1)], and methyl lævulate 2,4-dinitrophenylhydrazone, m. p. (double) 136—137° and 140·5—141·5° [Found: r.m.a. × 10^{-3}, (a) 207·1 (3C, 204·0); (b) 104·1 (2C, 100·4); (c) 1·9].

(iv) Oxidation with alkaline hydrogen peroxide [9] gave the dibasic acid (II), m. p. 97—99° [Found: r.m.a. × 10^{-3}, (a) 383·7 (6C, 407·9); (b) 282·1 (6C, 301·4); (c) 290·3 (3C, 306·4)].

(v) Oxidation of the dibasic acid (II) with lead tetra-acetate [9] gave (+)-α-methylbutyraldehyde 2,4-dinitrophenylhydrazone, m. p. 135—136° [Found: r.m.a. × 10^{-3}, (a) 132·1 (2C, 136·0); (b) 95·5 (2C, 100·4); (c) 99·2 (1C, 102·3)], barium carbonate [Found: r.m.a. × 10^{-3}, (a) 1·3; (b) 3·9; (c) 89·3 (1C, 102·3)] and 5-methyleneoct-2-enedioic acid (III), m. p. 113—116° [Found: r.m.a. × 10^{-3}, (a) 252·3 (4C, 272·0)].

(vi) Kuhn–Roth oxidation of (+)-α-methylbutyraldehyde 2,4-dinitrophenylhydrazone gave acetic acid, counted as its *p*-bromophenacyl ester, m. p. 85—86° [Found: r.m.a. × 10^{-3}, (a) 33·5 (0·5C, 34·0); (b) 47·4 (1C, 50·2); (c) 45·8 (0·5C, 51·1)]. Pyrolysis of lithium acetate gave barium carbonate (from lithium carbonate) [Found: r.m.a. × 10^{-3}, (a) 31·5 (0·5C, 34·0)] and iodoform [Found: r.m.a. × 10^{-3}, (a) 0·03].

[^{14}C]*Alternaric Acid from* [1-^{14}C]*Propionate.*—*Alternaria solani* was grown as above in the presence of sodium [1-^{14}C]propionate (0·5 mc in 10 l. of culture medium). The resulting alternaric acid monohydrate (Found: r.m.a. × 10^{-3}, 52·9) was hydrolysed as above with N-sulphuric acid to give barium carbonate (Found: r.m.a. × 10^{-3}, 4·59).

I am indebted to Mr. G. L. F. Norris who did the fermentations, and to Mr. B. D. Akehurst for technical assistance.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, AKERS RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, August 9th,* 1960.]

[9] Bartels-Keith, *J.*, 1960, 860.

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104. *Studies on Specific Chemical Fission of Peptide Links. Part III.* Fission of Peptides containing One Glutamic Acid Residue.*

By A. R. BATTERSBY and J. J. REYNOLDS.

Two α-glutamyl peptides (II) have been synthesised which differ in the bulk of the amino-acid residues adjacent to that of glutamic acid. A study is made of the cyclisation of the peptides by thionyl chloride to 1-acylpyrrolid-2-ones (III) and also of the subsequent alkaline hydrolysis of these products. The results obtained can be explained on the basis of steric effects.

It is shown, for four isomeric pairs, that methyl α- and γ-glutamate peptide esters can readily be distinguished by infrared measurements.

PART II * of this series described a procedure for the specific fission of peptide chains at those points where glutamic acid residues occur. The scheme involves the conversion of α-glutamyl peptides (as II) into 1-acylpyrrolid-2-ones (as III) which are then readily hydrolysed by dilute alkali; the same approach has been studied independently by Clayton, Kenner, and Sheppard.[1] Yields of the products of chain fission (at A in III) were sufficiently encouraging in our experiments to warrant a further study of this method.

* Part II, *J.*, 1956, 2076.

[1] Clayton, Kenner, and Sheppard, *J.*, 1956, 371.

XUM

The present renewed interest [2] in specific chemical fission of peptides prompts us to report the results, which were obtained in 1956—1957.

It seemed probable that cyclisation of α-glutamyl peptides (as II) to 1-acylpyrrolidones (as III) and the subsequent alkaline hydrolysis would both be affected by the size of closely situated groups. Accordingly, *N*-benzoylglycyl-α-DL-glutamyl(glycine hexylamide) (IIa) was prepared to serve as an example having the minimum bulk on each side of the glutamic acid residue; this is referred to below as the " glycine peptide." *N*-Benzoylglycyl-α-DL-glutamyl-(DL-phenylalanine amide) (IIb) was the selected case having a large group close to the α-carboxyl group of the glutamic acid; this we refer to as the " phenylalanine peptide."

The glycine peptide (IIa) was prepared by condensing *N*-benzoylglycyl-DL-glutamic acid with glycine hexylamide by the mixed-anhydride method [4] with the use of only one equivalent of ethyl chloroformate.[3] A good yield of the mixture of isomeric α- and γ-peptides (IIa and IVa respectively) was obtained which was fractionated by countercurrent distribution to give 65% of the required α-isomer (IIa). The more weakly acidic peptide was assigned the α-glutamyl structure (IIa) on the basis of previous experience [3,5] and this structure is confirmed below.

For the synthesis of the phenylalanine peptide, DL-phenylalanine amide [6] was made by condensing phthaloyl-DL-phenylalanine [7] with ammonia in a mixed anhydride reaction; the phthaloyl group was removed from the product in the usual way with hydrazine.[8] This route to the amide was used because a large amount of the starting material was available from other work. When DL-phenylalanine amide was condensed with *N*-benzoylglycyl-DL-glutamic acid by the method used for the peptide (IIa) above, a mixture of products was formed from which one diastereoisomer of the α-phenylalanine peptide (IIb) was isolated by a combination of countercurrent distribution and fractional crystallisation. The behaviour of this peptide during fractionation and the melting point of the isolated product give sound evidence for its homogeneity. One diastereoisomer of the γ-phenylalanine peptide (IVb) was isolated in the same way. As before, the weaker acid was assigned the α-glutamyl structure (IIb) and this assignment was later rigorously confirmed.

The glycine peptide (IIa) and the phenylalanine peptide (IIb) were both cyclised by thionyl chloride at −20° to give good yields of neutral products (89% and 63% respectively). However, fractional crystallisation of the neutral material in the glycine series showed it to be a mixture containing about 35% of the acylpyrrolidone (IIIa) together with the imide (Va). The imide (Va) was the only neutral product, formed in very low yield (5%), when the mixed carbonic anhydride (IIa; $CO{\cdot}O{\cdot}CO_2Et$ in place of CO_2H) derived from the glycine peptide (IIa) was allowed to cyclise at low temperature. Surprisingly, the γ-peptide in the glycine series (IVa) was quantitatively recovered after being treated under the same conditions as the α-isomer (IIa) in a mixed carbonic anhydride reaction.

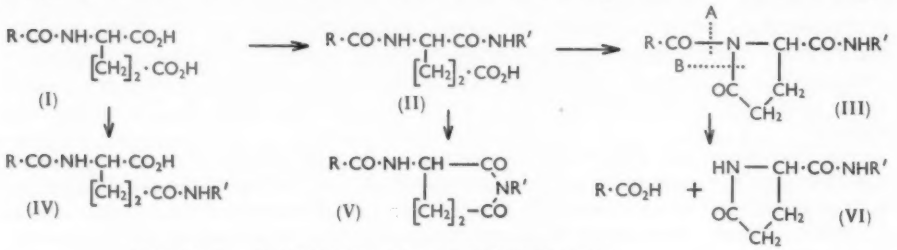
In accord with earlier results,[1,3,5] alkaline hydrolysis of the imide (Va) gave a mixture consisting of 79% of the γ-peptide (IVa) and 21% of the α-peptide (IIa). These accounted for 96% of the imide used and a negligible amount of neutral material was formed.

The neutral product resulting from cyclisation of the phenylalanine peptide (IIb) with thionyl chloride was almost entirely the acylpyrrolidone (IIIb); a search for the imide

[2] Schmir, Cohen, and Witkop, *J. Amer. Chem. Soc.*, 1959, **81**, 2228; Corey and Haefele, *J. Amer. Chem. Soc.*, 1959, **81**, 2225; Ramachandran and Witkop, *J. Amer. Chem. Soc.*, 1959, **81**, 4028.
[3] Battersby and Robinson, *J.*, 1956, 2076.
[4] Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874; Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 3547; Wieland and Bernhard, *Annalen*, 1951, **572**, 190.
[5] Battersby and Robinson, *J.*, 1955, 259.
[6] Koenigs and Mylo, *Ber.*, 1908, **41**, 4439.
[7] Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856.
[8] Ing and Manske, *J.*, 1926, 2348.

XUM

yielded only a trace of material which could be this product and the amount was insufficient for characterisation. This result is in striking contrast to the predominant formation of imide from the glycine peptide (IIa) and its seems probable that this is due to the bulk of the phenylalanine residue. The electronic effect of the benzyl side chain on the nitrogen



Series (a): R = Ph·CO·NH·CH_2, R′ = CH_2·CO·NH·$[CH_2]_5$·Me
Series (b): R = Ph·CO·NH·CH_2, R′ = $CH(CH_2Ph)$·CO·NH_2
Series (c): R = C_7H_7·SO_2·NH·CH_2·CO·NH·CH_2, R′ = $CH(CH_2Ph)$·CO·NH·C_6H_{11}

atom involved in imide formation may also assist, but that effect is probably small; for example, one can compare the shift in acidic strength from acetic acid (pK_a 4·74) to β-phenylpropionic acid [9] (pK_a 4·66).

The above formation of acylpyrrolidones from the glycine and phenylalanine peptides confirms the structures (IIa) and (IIb) respectively assigned to them on the basis of acidic strengths.

Our main interest in studying the alkaline hydrolysis of the two acylpyrrolidones (IIIa) and (IIIb) was centred on the extent of the fission (at A in III); the acidic products, which by analogy with Battersby and Robinson's results [3] should contain the α- and γ-peptides (as II and IV respectively) in addition to *N*-benzoylglycine, were not examined. In the glycine series, hydrolysis of the acylpyrrolidone (IIIa) by 0·1N-sodium hydroxide in aqueous dioxan yielded approximately 50% of the 5-oxo-DL-pyrrolidone (VIa), so giving a measure of the chain fission. Under the same conditions, the acylpyrrolidone (IIIb) in the phenylalanine series gave approximately 40% of the corresponding product (VIb) of chain fission. Both pyrrolidones (VIa) and (VIb) showed carbonyl absorption in the infrared spectrum close to 1700 $cm.^{-1}$, in agreement with the value recorded by Barrass and Elmore [10] for a similar pyrrolidone.

Clayton, Kenner, and Sheppard [1] have studied a close analogue (IIIc) of the acylpyrrolidone derived from the phenylalanine peptide (IIb); their material differs from ours only in having toluene-*p*-sulphonylglycyl in place of the benzoyl group and cyclohexyl in place of the n-hexyl residue. However, hydrolysis of their material (IIIc) under conditions which were similar to ours regenerated 90% of the starting material (IIc). A possible explanation of these differing results is that the highly polar toluene-*p*-sulphonyl group is interacting with the acyl-carbonyl group of the acylpyrrolidone (IIIc); a study of the analogue having benzoyl in place of the toluene-*p*-sulphonyl group would therefore be of interest.

Since a higher proportion of chain fission than that achieved above is very desirable, a study was made of the effect of different solvents and one other base on the hydrolysis. The results were not significantly different from those above when either aqueous tetrahydrofuran or dimethylformamide was used. This is in contrast to the appreciable effect that changes of solvent had on the hydrolyses of related compounds.[11] In addition, the hydrolysis of our acylpyrrolidones does not occur at room temperature at a significant rate in aqueous dioxan containing triethylamine.

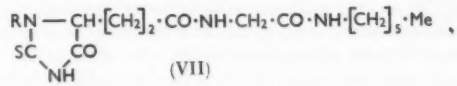
[9] Dippy, *Chem. Rev.*, 1939, **25**, 151.
[10] Barrass and Elmore, *J.*, 1957, 4830.
[11] Wieland and Weidenmuller, *Annalen*, 1955, **597**, 111.

Compound	Absorption bands in 1600—1800 cm.$^{-1}$ region (Nujol mull)	Ester >C=O absorption (cm.$^{-1}$) ($CHCl_3$ solution)
II; Me ester, R = Ph, R′ = CH_2·CO·NH·$[CH_2]_5$·Me	1617(sh)s, 1640vs, 1657vs, 1670(sh)s, 1751s	1728s
IV; Me ester, R = Ph, R′ = CH_2·CO·NH·$[CH_2]_5$·Me	1617(sh)m, 1650vs, 1690(sh)m, 1761s	1742s
II; Me ester, R = Ph·CO·NH·CH_2, NHR′ replaced by NEt_2	1615w, 1651vs, 1667(sh)s, 1681m, 1742s, 1751s	1733s
IV; Me ester, R = Ph·CO·NH·CH_2, NHR′ replaced by NEt_2	Amorphous	1757s
IIa; Me ester	1616(sh)m, 1652vs, 1680(sh)s, 1756s	1748s
IVa; Me ester	1615m, 1650vs, 1667vs, 1676(sh)s, 1701(sh)m, 1751s	1758s
IIb; Me ester	1619(sh)s, 1633vs, 1652(sh)s, 1669(sh)s, 1689s, 1745s	Insoluble
IVb; Me ester	1615(sh)s, 1649vs, 1660(sh)vs, 1683s, 1705s, 1760s	Insoluble
IIIa	1617w, 1659vs, 1702s, 1718(sh)m, 1767s	
Va	1617(sh)m, 1638(sh)s, 1658vs, 1677vs, 1704s, 1751w	
VIa	1640(sh)s, 1660vs, 1676(sh)s, 1705vs	
IIIb	1614w, 1651vs, 1690vs, 1701(sh)s, 1744s, 1761s	
VIb	1655s, 1678(sh)s, 1688s	
VII; R = Ph·CO	1648vs, 1683s, 1754s	
VII; R = H	1650vs, 1711(sh)s, 1731vs	

The foregoing work supports the conclusions [3] drawn from earlier experiments. However, it is now clear that the results are markedly affected by changes in the environment of the glutamic acid residue. Probably, therefore, the acylpyrrolidone method should only be considered for peptides containing one glutamic acid group. The resultant mixture would then be sufficiently simple to allow the peptides that had not undergone fission to be recycled through the process to increase the yield.

The infrared spectra of some of our peptides are of interest. It has been found that the ester-carbonyl absorptions of α-glutamyl peptide methyl esters (esters of II) lie 10—20 cm.$^{-1}$ lower than those of the γ-glutamyl isomers (esters of IV); the esters shown in the Table were prepared from the corresponding acids by using diazomethane. The lower frequency of the carboxylic acid band for α-glutamyl peptides than for the γ-isomers has been pointed out previously by Clayton, Kenner, and Sheppard,[1] but in the case of the free acids there is considerable variation with structure which the authors reasonably ascribe to differences in the hydrogen bonding of the carboxyl group. The esters studied so far give sharp absorption peaks with somewhat steadier values and this approach promises to be a simple one for orienting α- and γ-glutamyl peptides when both isomers are available.

Experiments have been carried out on the reactivity of two of the γ-glutamyl peptides (IV) prepared in this work towards diphenyl phosphorisothiocyanatidate.[12] *N*-Benzoyl-γ-DL-glutamyl(glycine hexylamide) [5] (IV; R = Ph, R′ = CH_2·CO·NH·$[CH_2]_5$·Me) was smoothly converted by this reagent into 65% of the thiohydantoin (VII; R = Ph·CO);



(VII)

hydrolysis of this product with aqueous alkali gave 77% of the theoretical yield of benzoic acid together with the hydantoin (VII; R = H). However, the peptide (IVa) gave little or none of the expected acylthiohydantoin when treated with the same reagent under the same or similar conditions.

[12] Kenner, Khorana, and Stedman, *J.*, 1953, 673.

XUM

Experimental

For general directions see Part II.[3]

N-Benzoylglycyl-α- and -γ-DL-glutamyl(glycine Hexylamides) (IIa) *and* (IVa).—Ethyl chloroformate (2·4 ml., 1 equiv.) was added to a stirred solution of *N*-benzoylglycyl-DL-glutamic acid [3] (7·72 g.) and triethylamine (3·5 ml., 1 equiv.) in chloroform (50 ml.) and dimethylformamide (50 ml.) at 0°. After 20 min., a solution of glycine hexylamide hydrochloride [5] (4·87 g., 1 equiv.) and triethylamine (3·5 ml.) in chloroform (20 ml.), dimethylformamide (5 ml.), and water (5 ml.) was added and stirring was continued for 3 hr. at 0°. The solvents were evaporated and the residue was partitioned between water (50 ml.) and ethyl acetate (100 ml., and, after filtration and separation, with 200 ml.). The aqueous phase was then adjusted to pH 2 with concentrated hydrochloric acid, and the precipitated solid (4·71 g.) was collected and dried. The combined ethyl acetate extracts were shaken with 0·1N-sodium hydroxide (2 × 150 ml.), and the alkaline extract was acidified to precipitate crystals (0·78 g.). The filtrate was extracted with ethyl acetate (2 × 150 ml.), and this extract was dried and evaporated to give more solid (1·42 g.).

The combined solids (6·81 g.) were fractionated by countercurrent distribution (scattered in the first 11 tubes; 124 transfers) between ethyl acetate (4 vol.), butan-1-ol (1 vol.), and aqueous phosphate buffer (5·6 vol.); [from 0·5M-KH_2PO_4 (4 vol.) and 0·5M-K_2HPO_4 (2·8 vol.)]. Two completely separated peaks were obtained (*K* 0·22, 34%; *K* 0·94, 46%). The organic layer from tubes 13—42 (*K* 0·22) was extracted with an excess of N-sodium hydroxide, and this extract was combined with the aqueous layer from these tubes. This solution was adjusted to pH 10 with N-sodium hydroxide and washed with ethyl acetate. The aqueous solution was acidified and left overnight; *N-benzoylglycyl-γ-DL-glutamyl(glycine hexylamide)* (IVa) was precipitated as prisms (2·03 g.), m. p. 200—201°, unchanged by further recrystallisation from ethanol (Found: C, 58·9; H, 7·0; N, 12·3%; equiv., 440. $C_{22}H_{32}N_4O_6$ requires C, 58·9; H, 7·2; N, 12·5%; equiv., 448). A further quantity of the same peptide (0·28 g.), m. p. 200°, was obtained by extraction of the above filtrate with ethyl acetate.

N-Benzoylglycyl-α-DL-glutamyl(glycine hexylamide) (IIa), recovered in the same way from tubes 45—95 (*K* 0·94), formed needles (3·14 g.), m. p. 162—163°, unchanged by further recrystallisation from ethanol (Found: C, 59·0; H, 7·4; N, 12·5%; equiv., 437).

Cyclisation of N-Benzoylglycyl-α-DL-glutamyl(glycine Hexylamide) (IIa).—(a) *By thionyl chloride.* This peptide (1·86 g.) was treated with purified thionyl chloride (50 ml.) at 0° for 125 hr. Evaporation of the thionyl chloride at 0° left a gum which was partitioned between 5% aqueous sodium hydrogen carbonate (150 ml.) and ethyl acetate (400 ml., and, after separation, with 250 ml.). The organic extract was washed with water, dried, and evaporated to leave a brown crystalline residue (1·60 g., 89%) which was recrystallised from ethyl acetate to give *N-benzoylglycyl-5-oxo-DL-pyrrolidine-2-carbonyl(glycine hexylamide)* (IIIa) (0·58 g.) as needles, m. p. 193—194° raised by recrystallisation from the same solvent to 195—196° (Found: C, 61·4; H, 6·9; N, 13·6. $C_{22}H_{30}N_4O_5$ requires C, 61·4; H, 7·0; N, 13·0%).

Evaporation of the ethyl acetate mother-liquors above left the imide, *DL-α-N-benzoylglycyl-aminoglutaryl(glycine hexylamide)* (Va), as nodules (0·90 g.), m. p. 150—153°, changed by recrystallisation from ethyl acetate to 150° (Found, in material dried at 130°: C, 61·2; H, 6·8; N, 13·3. $C_{22}H_{30}N_4O_5$ requires C, 61·4; H, 7·0; N, 13·0%).

(b) *By the mixed carbonic anhydride method.* A stirred solution of the peptide (IIa) (0·15 g.) and triethylamine (0·047 ml., 1 equiv.) in dioxan (15 ml.) and dimethylformamide (5 ml.) was treated at 0° with ethyl chloroformate (0·032 ml., 1 equiv.). After 20 min. at 0°, the solution was stirred for 2 hr. as the cooling-bath warmed to room temperature, and was then kept overnight. The organic solvents were evaporated and the residue was partitioned between 0·1N-hydrochloric acid (30 ml.) and ethyl acetate (2 × 50 ml.). The combined ethyl acetate solutions were extracted with an excess of 5% aqueous sodium hydrogen carbonate (40 ml.), washed with water, dried, and evaporated to give a neutral fraction (7·5 mg., 5%). This crystallised from ethyl acetate to give the imide (Va), m. p. 151°; its infrared spectrum was identical with that of the sample prepared as under (a).

Alkaline Hydrolysis of N-Benzoylglycyl-5-oxo-DL-pyrrolidine-2-carbonyl(glycine Hexylamide) (IIIa).—The acylpyrrolidone (95·2 mg.) in dioxan (10 ml.) and water (3·5 ml.) was titrated with 0·1N-sodium hydroxide (2·25 ml., 1 equiv.); all the alkali was consumed in 5 min. The dioxan was evaporated and the residue partitioned between water (10 ml.) and ethyl acetate

XUM

(2 × 50 ml.). The organic extract was washed with an excess of 10% aqueous potassium carbonate solution (40 ml.), with water, and then dried and evaporated to give a crystalline residue (32·2 mg., 54%), m. p. 95—96°. Recrystallisation twice from ethyl acetate gave 5-oxo-DL-pyrrolidine-2-carbonyl(glycine hexylamide), m. p. 100° (Found in material dried at 110°: C, 57·5; H, 8·4; N, 15·3. Calc. for $C_{13}H_{23}N_3O_3$: C, 57·9; H, 8·6; N, 15·6%). This material gave an infrared spectrum identical with that of the slightly impure material obtained by Battersby and Robinson.[3]

When the acylpyrrolidone was similarly hydrolysed in 1 : 15 aqueous tetrahydrofuran or in dimethylformamide, 53% and 54% respectively of neutral material was obtained.

Alkaline Hydrolysis of DL-α-N-*Benzoylglycylaminoglutaryl*(*glycine Hexylamide*) (Va).—A solution of the imide (Va) (0·22 g.) in dioxan (12 ml.) and water (6 ml.) was titrated with 0·1N-sodium hydroxide (5·14 ml., 1 equiv.) during 5 min. The products were isolated as above to give neutral material (7·1 mg.) and an acidic fraction (0·223 g., 96%). The latter was fractionated by countercurrent distribution (75 transfers) in the system used in the first experiment described above; two separate peaks (*K* 0·30, 79%; *K* 1·2, 21%) were obtained. The solute from the former (tubes 9—30) was recovered as before and crystallised from ethanol, to give the γ-glutamyl peptide (IVa), m. p. and mixed m. p. 200—201°. The second peak (tubes 31—51) similarly yielded the slightly impure α-glutamyl peptide (IIa), m. p. 145°, mixed m. p. raised to 151—152°.

DL-*Phenylalanine Amide*.—A stirred solution of phthaloyl-DL-phenylalanine [7] (25 g.) and triethylamine (11·83 ml.) in dioxan (200 ml.) and chloroform (100 ml.) was treated with ethyl chloroformate (8·1 ml., 1 equiv.) at 0°. After 20 min., ammonia (30 ml.; *d* 0·880) was added, and the stirring was continued for 4 hr. at 0°. The mixture was then allowed to warm to room temperature overnight. The precipitated solid (21·48 g.), m. p. 230°, was recrystallised from ethyl acetate to give *phthaloyl-DL-phenylalanine amide* as needles, m. p. 231° (Found: C, 69·8; H, 4·8; N, 9·6. $C_{17}H_{14}N_2O_3$ requires C, 69·4; H, 4·8; N, 9·5%). The aqueous mother-liquor (above) was evaporated and the residue partitioned between water (100 ml.) and ethyl acetate (400 ml.). The organic extract was washed with 0·5N-hydrochloric acid (100 ml.), water (100 ml.), 5% aqueous sodium hydrogen carbonate (100 ml.) and water (100 ml.) and then dried and evaporated to give more phthaloyl-DL-phenylalanine amide (1·78 g.), m. p. 230°.

A solution of this product (11·87 g.) in ethanol (280 ml.) was heated under reflux with hydrazine hydrate (2·08 ml., 1 equiv.) for 1 hr., then cooled, filtered, and evaporated to dryness. The resultant solids were combined and treated with water (40 ml.) and N-hydrochloric acid (60 ml., 1·5 equiv.) at 50° for 5 min. After being filtered, the solution was evaporated until crystallisation started; then an excess of saturated aqueous potassium carbonate solution was added; the precipitated crystals of DL-phenylalanine amide were collected (3·83 g., 58%), m. p. 136—137·5° raised by recrystallisation from chloroform to 137—138° [Koenigs and Mylo [6] record m. p. 138—140° (corr.)].

N-*Benzoylglycyl-α- and -γ-*DL-*glutamyl*(*phenylalanine Amides*) (IIb) *and* (IVb).—Ethyl chloroformate (2·74 ml., 1 equiv.) was added to a stirred solution of *N*-benzoylglycyl-DL-glutamic acid [3] (8·76 g.) and triethylamine (3·94 ml., 1 equiv.) in chloroform (250 ml.) and dimethylformamide (250 ml.) at 0°. After 20 min., a solution of DL-phenylalanine amide (4·61 g., 1 equiv.) and triethylamine (3·94 ml.) in chloroform (190 ml.), dimethylformamide (25 ml.), and water (30 ml.) was added and stirring continued for 3 hr. at 0°. The solvents were evaporated and the residue was partitioned between water (170 ml.) and ethyl acetate (230 ml.), the aqueous layer being adjusted to pH 2. Crystals slowly separated which were collected (3·51 g.), m. p. 205—208°. The aqueous layer was extracted with more ethyl acetate (2 × 150 ml.), and the combined organic solutions were then shaken with an excess of 0·5N-sodium hydroxide (3 × 200 ml.). Acidification of the alkaline solution gave crystals (2·61 g.), m. p. 170—180°, and the mother-liquor from them was extracted with ethyl acetate (3 × 500 ml.), to give an amorphous acidic fraction (5·17 g.).

A portion of the combined crystalline material (4·75 g.) was fractionated by countercurrent distribution (scattered in the first ten tubes) between ethyl acetate (4 vol.), butan-1-ol (1 vol.), and aqueous phosphate buffer (5·33 vol.) [from 0·5M-K_2HPO_4 (1·33 vol.) and 0·5M-KH_2PO_4 (4 vol.)]. After 18 transfers, solid *A* (0·96 g.) separated in several tubes; this was collected and the solutions were returned to the correct tubes in the machine before the fractionation was continued. After 90 transfers, two completely separated peaks were obtained (*K* 0·20, 16%; *K* 1·20, 62%) together with a coloured forerun which was rejected.

XUM

The solute from the former peak (tubes 4—26) was recovered as above and crystallised from ethanol, to give the *γ-phenylalanine peptide* (IVb) (0·22 g.), m. p. 177—178°, unchanged by further recrystallisation (Found: C, 60·6; H, 6·2; N, 12·45. $C_{23}H_{26}N_4O_6$ requires C, 60·8; H, 5·8; N, 12·3%).

The solute from the major peak (tubes 29—64) crystallised from ethanol, to give the *α-phenylalanine peptide* (IIb) (1·94 g.), m. p. 219°, raised by recrystallisation from ethanol to 224—225·5° (Found: C, 60·5; H, 5·7; N, 12·5%).

Solid *A* was shown to be the α-phenylalanine peptide (IIb) by m. p. and infrared spectrum.

N-*Benzoylglycyl*-5-*oxo*-DL-*pyrrolidine*-2-*carbonyl*-(DL-*phenylalanine Amide*) (IIIb).—A solution of the phenylalanine peptide (IIb) (1·56 g.) in thionyl chloride (16 ml.) was kept for 72 hr. at 0° and then evaporated at 0°. The residual gum was partitioned between 5% aqueous sodium hydrogen carbonate (300 ml.) and ethyl acetate (1 l. and after separation, with 300 ml.); evaporation of the combined ethyl acetate extracts gave a neutral gum (0·94 g., 63%). This crystallised from ethyl acetate to give the *oxopyrrolidine* (IIIb) as prisms (0·83 g.), m. p. 241—242° (Found: C, 63·3; H, 5·5; N, 13·35. $C_{23}H_{24}N_4O_5$ requires C, 63·3; H, 5·5; N, 12·8%).

Evaporation of the mother-liquors gave a solid (80 mg.) which after repeated crystallisation from ethyl acetate had m. p. 190—191°.

Hydrolysis of N-*Benzoylglycyl*-5-*oxo*-DL-*pyrrolidine*-2-*carbonyl*-(DL-*phenylalanine Amide*) (IIIb).—This material (0·44 g.) in dioxan (22 ml.) was titrated with 0·1N-sodium hydroxide (10·31 ml., 1·03 equiv.); all the alkali was consumed in 10 min. The dioxan was evaporated and the residue was fractionated as for the glycine analogue above. The neutral fraction (120 mg., 43%) crystallised from ethanol to give 5-*oxo*-DL-*pyrrolidine*-2-*carbonyl*-(DL-*phenylalanine amide*), m. p. 238° (Found: C, 61·9; H, 6·3. $C_{14}H_{17}N_3O_3$ requires C, 61·1; H, 6·2%).

2-(N-*Benzoyl*-5-*thiohydantoinyl*)*propionyl*(*glycine Hexylamide*) (VII; R = Ph·CO).—A solution of *N*-benzoyl-*γ*-DL-glutamyl(glycine hexylamide) (IV; R = Ph, R′ = CH_2·CO·NH·$[CH_2]_5$·Me) (275 mg.) in acetonitrile (4 ml.) and triethylamine (0·11 ml., 1 equiv.) was shaken with diphenyl phosphorisothiocyanatidate [12] (0·23 g., 1 equiv.) for 48 hr. at room temperature. The precipitate (198 mg., 65%) was collected and recrystallised from 30% aqueous ethanol, to give the *thiohydantoin* (VII; R = Ph·CO), m. p. 197° (Found: C, 58·4; H, 6·8; N, 12·0; S, 7·0. $C_{21}H_{28}N_4O_4S$ requires C, 58·3; H, 6·5; N, 12·9; S, 7·4%).

Alkaline Hydrolysis of the Thiohydantoin (VII; R = Ph·CO).—This material (176 mg.) was shaken with 0·02N-sodium hydroxide (40·8 ml., 2 equiv.), and the resultant solution was kept at 20° for 30 min. Addition of dilute hydrochloric acid to pH 6 precipitated a solid (102 mg.) which was recrystallised from ethanol, to give 2-(5-*thiohydantoinyl*)*propionyl*(*glycine hexylamide*) (VII; R = H), m. p. 177° (Found: C, 50·8; H, 7·3. $C_{14}H_{24}N_4O_3S$ requires C, 51·2; H, 7·4%).

After the aqueous solution has been extracted with ethyl acetate which removed more thiohydantoin (VII; R = H) (46 mg.), it was acidified with dilute hydrochloric acid and extracted with light petroleum (b. p. 40—60°; 1·5 l.). This extract was washed with water, dried, and evaporated to give benzoic acid (38·5 mg., 77%), m. p. 116—118°, mixed m. p. 118—120°.

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THE UNIVERSITY, BRISTOL. [*Received, June 7th*, 1960.]

XUM

105. *The Alkaline Degradation of Glucose and of Some of its Acetyl Derivatives.*

By W. M. Corbett and A. Margaret Liddle.

The alkaline degradation of glucose has been studied in detail. In solutions of hydroxyl-ion concentration 0·01—0·05 g.-ions per l., the yield of total acid is inversely related to the hydroxyl-ion concentration, being between 2·5 and 1·5 equiv. The increase in acidity is mainly due to an increase in yield of formic acid. It has also been shown that gluco-metasaccharinic is the main saccharinic acid, although at high concentrations of calcium ion the yield of glucosaccharinic acid becomes comparable. In addition, the degradation of tetra-*O*-acetyl-2-hydroxy-D-glucal and the early stages of degradation of penta-*O*-acetyl-D-glucose, 2,3,4,6-tetra-*O*-acetyl-D-glucose, and penta-*O*-acetyl-*aldehydo*-D-glucose have been briefly studied.

In their study of the degradation of cellobiose by calcium hydroxide, Corbett and Kenner [1] found that the yield of acid estimated from the alkali consumed was greater than that determined from the acidity of the solution after removal of calcium ions by ion-exchange resin. Whereas the latter method gave a value close to the expected one of 2·6 equiv. for complete decomposition to acidic products (1 equiv. from the saccharinic acid produced by β-alkoxycarbonyl elimination, and 1·6 equiv. from the glucose thus formed [2]), the former gave a value between 3 and 4 equiv. It was therefore suggested that the yield of acid estimated by the ion-exchange resin method was the correct one, and that the difference

Table 1. *Degradation of cellobiose by saturated lime-water at* 25°.

Time (hr.)	Cellobiose decompd. (equiv.)	Monoses produced (equiv.)	Acid yield (equiv.) Calc.*	Back-titre method	Resin method
1	0·00	0·00	0·00	0·01	0·00
2	0·01	0·01	0·01	0·02	0·01
3	0·02	0·02	0·03	0·04	0·02
4	0·02	0·04	0·02	0·05	0·04
6	0·05	0·06	0·05	0·09	0·07
10·5	0·17	0·18	0·17	0·20	0·17
24	0·44	0·45	0·44	0·51	0·50
31	0·54	0·53	0·55	0·67	0·64
46	0·67	0·64	0·71	0·89	0·86
53	0·73	0·65	0·86	0·98	0·94
71	0·82	0·72	0·99	1·13	1·09
144	0·84	0·69	1·09	1·29	1·25
240	0·90	0·74	1·17	1·44	1·41

* Calc. by assuming that cellobiose decomposes to 1 equiv. of acid and 1 mol. of glucose which further decomposes to 1·6 equiv. of acid.

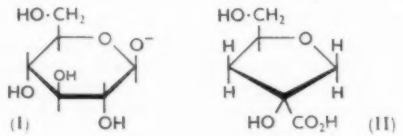
between the two methods was due to absorption of calcium hydroxide by undegraded cellobiose. This aspect of the degradation of cellobiose has now been re-investigated in detail.

Examination of the resin method showed that results previously obtained were low because of lactonisation of saccharinic acids by the resin. When modified to eliminate lactone formation, the resin method gave yields of acid in agreement with those determined from the alkali consumed (Table 1). The observed excess of acid over the expected value of 2·6 equiv. is therefore real and is not due to absorption of calcium hydroxide. The directing influence of the substituent at the 4-position of the reducing glucose unit on the degradation of cellobiose to one molecule of saccharinic acid and one molecule of glucose is shown by the fact that, until the later stages of the reactions, the acid produced is

[1] Corbett and Kenner, *J.*, 1955, 1431.
[2] Kenner and Richards, *J.*, 1954, 1784.

XUM

approximately equal to the disaccharide decomposed. It therefore appears that degradation of the glucose formed from cellobiose is responsible for the excess of acid. This glucose will exist initially as the glucosyloxy-ion (I), which could possibly react with alkali to give more acid than does the normal complex mixture of ions which occurs in alkaline solutions of glucose. A direct proof of this cannot be achieved because of the difficulty of obtaining glucosyloxy-ions. However, since deacetylation of acetates produces the ion of the corresponding alcohol as an intermediate, a study has been made of the action of alkali on various glucose acetates.



Penta-*O*-acetyl-α-D-glucose underwent deacetylation, at rates dependent on its crystal size, when suspended in saturated oxygen-free lime-water (Fig. 1A) or in a suspension of calcium hydroxide (Fig. 1B). The rapid formation of acid did not cease when deacetylation was complete but continued until an acid yield of *ca.* 5·2 equiv. was reached; the rate then decreased to that found for glucose.[2] Penta-*O*-acetyl-β-D-glucose in saturated lime-water behaved in a similar manner. In contrast, the α-acetate in 0·05N- and 1·0N-sodium hydroxide underwent deacetylation followed by normal degradation (Fig. 1C and 1D, respectively). The continued rapid production of acid after deacetylation by lime-

FIG. 1. *Degradation of penta-*O*-acetyl-*D*-glucose by* (A) 0·045N-*lime-water*, (B) *suspension of lime*, (C) 0·050N-*sodium hydroxide, and* (D) 1·00N-*sodium hydroxide.*

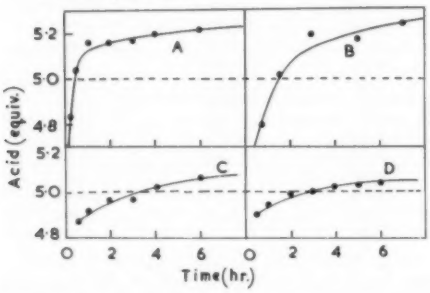
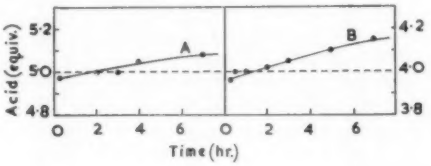


FIG. 2. (A) *Degradation of penta-*O*-acetylaldehydo-*D*-glucose by* 0·044N-*lime-water*. (B) *Degradation of* 2,3,4,6-*tetra-*O*-acetyl-β-*D*-glucose by* 0·041N-*lime-water.*



water is apparently due to the intermediate formation and subsequent degradation of the glucosyloxy-ion since penta-*O*-acetyl-*aldehydo*-D-glucose and 2,3,4,6-tetra-*O*-acetyl-β-D-glucose behaved normally (Figs. 2A and B, respectively). It appears that the glucosyloxy-ion is converted into the normal mixture of glucose ions within 2 hr. This explains the fall in rate of acid production to that observed for glucose.

Paper-chromatography of the initial non-volatile acidic components of the lime-water degradation of penta-*O*-acetyl-D-glucose indicated that essentially only one acid (R_L 0·31; movement relative to lactic acid) was present. It resembled a reductone rather than a carboxylic acid, since its behaviour towards chromatographic sprays was very similar to that of ascorbic acid. Moreover, it was unaffected by alkali and therefore was not an intermediate. In agreement with these quantitative experiments, the acid of R_L 0·31 could not be detected among the degradation products from penta-*O*-acetyl-D-glucose in 0·05N- or 1·0N-sodium hydroxide, or those from penta-*O*-acetyl-*aldehydo*- and tetra-*O*-acetyl-D-glucose in lime-water. However, it was formed from cellobiose by lime-water.

The acid was obtained only in very small amounts contaminated with glucometasaccharinic acid and chromatographically slow-moving acids.

The neutral products first formed by lime-water from penta-*O*-acetyl-D-glucose reacted slowly with acidic 2,4-dinitrophenylhydrazine to give a complex mixture from which was isolated a compound A. Since this was not obtained similarly from glucose it was apparently derived from a compound resulting from the glucosyloxy-ion. Under similar conditions, lactose should then give an analogous dinitrophenylhydrazine derivative, provided that the $C_{(4)}$ centre of the galactose moiety does not lose its asymmetry. Such a compound, B, was indeed isolated.

The constants of compound A are similar to those of the dinitrophenylhydrazine derivative of 2-hydroxy-D-glucal,[3] and on admixture there was no depression of the albeit indefinite melting point. The *X*-ray powder photographs of the two compounds differed (though this in turn could be due to different crystalline forms). The similarity is of interest since it has been suggested that 2-hydroxyglucal may be an intermediate in the alkaline degradation of glucose.[4] Accordingly, the acidic products from the alkaline

TABLE 2. *The degradation of 2-hydroxy-D-glucal tetra-acetate by lime-water at 25°: acid yields.*

0·009N-Lime-water		0·044N-Lime-water		0·044N-Lime-water		Suspension	
Time (hr.)	Equiv. of acid	Time (hr.)	Equiv. of acid	Time (hr.)	Equiv. of acid	Time (hr.)	Equiv. of acid
0·5	4·65	0·33	4·39	6	5·02	0·5	4·61
1	4·92	0·75	4·75	24	5·18	1	4·84
3	5·25	1	4·81	48	5·22	4	4·90
7·5	5·55	2	4·92			7	4·95
24	5·55					24	4·95

TABLE 3. *Degradation of 2-hydroxy-D-glucal tetra-acetate by lime-water at 25°: composition of acids.*

	0·011N-Lime-water	Suspension		0·011N-Lime-water	Suspension
Equiv. acids	5·26	5·07	Non-volatile acids (cont.):		
Volatile acids	4·00	4·03	lactone, R_L 0·67 ...	0·18	0·08
Non-volatile acids:			lactone, R_L 0·45 ...	0·15	0·25
lactic	0·02	0·02	lactone, R_L 0·05 ...	0·06	0·03
dihydroxybutyric ...	0·11	0·05	acid, R_L 0·51	0·42	0·18
glycollic	0·04	0·03	acid, R_L 0·31	0·18	0·24
lactone, R_L 0·82 ...	0·06	0·03	acid, R_L 0·05	0·04	0·03

degradation of 2-hydroxyglucal tetra-acetate have been briefly studied. Degradation occurs very readily (Table 2: the difference in rates is probably due to differences in crystal size, as observed for penta-*O*-acetylglucose), but the final yield of acid appears to vary inversely with the strength of alkali. An approximate analysis of the exceedingly complex mixture of acids was made by thick-paper chromatography, but many of the products could not be identified (Table 3). The main component was an acid of R_L 0·51 which could not be completely separated from an acid of R_L 0·31. The former corresponds to the acid, probably tetrahydro-3-hydroxy-5-hydroxymethylfuran-3-carboxylic acid[5] (II), produced by the alkaline degradation of 2-hydroxycellobial. Because this acid of R_L 0·31 does not react instantaneously with permanganate and also from analyses of the acidic degradation products of glucose (see below), it is concluded that 2-hydroxyglucal is not an intermediate in the alkaline degradation of glucose. Consequently compound A is not the 2,4-dinitrophenylhydrazine derivative of 2-hydroxy-D-glucal.

[3] Corbett, *J.*, 1959, 3213.
[4] Kusin, *Ber.*, 1936, **69**, 1041.
[5] Corbett and Kidd, *J.*, 1959, 1594.

XUM

The small amount of acid of R_L 0·31 produced (presumably) from glucosyloxy-ions (Fig. 1) cannot explain the excess of acid produced from the glucose moiety of cellobiose. In the cellobiose experiments the strength of the lime-water fell to *ca.* 0·01N before degradation of glucose became appreciable. As this was a quarter of the concentration used in the comparable experiment with glucose,[2] the effect of alkali concentration on the yield of acid from glucose has been studied.

Glucose was degraded with lime-water of varying strength, and the yields of acid were plotted against amounts of hexose decomposed (as measured by fall in reducing power). Extrapolation of the resulting straight lines gave values for complete decomposition. The results (Fig. 3 and Table 4) show that the total yield of acid is inversely related to the initial concentration of the lime-water and is independent of the glucose concentration.

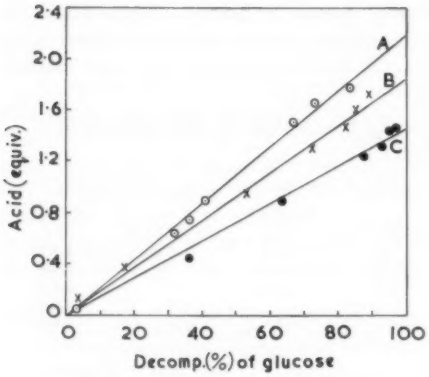


FIG. 3. *Degradation of glucose by* (A) 0·013N-*lime-water*, (B) 0·025N-*lime-water, and* (C) *suspension of lime.*

Further, this inverse relation is not peculiar to lime-water, but applies also to barium and sodium hydroxides (Table 4). From experiments in which the ionic strength of sodium hydroxide solutions was varied, it was shown that the yield of acid is inversely related to hydroxyl-ion concentration, and is independent of ionic strength (Table 4). Galactose, fructose, and xylose (Table 4) also show this inverse relation of yield of acid to alkali strength.

Since a number of competing reactions are involved in the alkaline degradation of unsubstituted sugars, one or more of these must be preferentially accelerated or retarded when the strength of alkali is decreased. In contrast, the degradation as a whole is catalysed by calcium ions, the half-life for glucose in 0·046N-lime-water and -sodium hydroxide being 50 and 350 hr., respectively. This is in agreement with the work of Kenner and Richards on substituted sugars.[6] However, with unsubstituted sugars the Lobry de Bruyn–Alberda van Ekenstein transformation is more important than with substituted sugars because degradation is more rapid in the latter case. It has been found that calcium ions have no influence on this transformation since glucose in both saturated lime-water and 0·04N-sodium hydroxide gives an equilibrium mixture of glucose 66%, fructose 33%, and mannose 1%.[7]

In order that the effect of hydroxyl and calcium ions might be investigated in more detail, the acidic degradation products of glucose with 0·01N-calcium hydroxide, a suspension of calcium hydroxide, and 0·05N-sodium hydroxide were analysed (Table 5). The non-volatile acids were separated by paper chromatography, but as the percentage elution from the paper was only of the order of 50%, the accuracy of the results is low. Nevertheless, there are marked differences in the composition of the complex mixtures of

[6] Kenner and Richards, *J.*, 1957, 3019.
[7] Cf. Speck, *Adv. Carbohydrate Chem.*, 1958, **13**, 63.

acids. Thus, substantially less of the unknown acid of R_L 0·48 is formed in 0·05N-alkali than in 0·01N-alkali. Its structure has not been determined because it could not be obtained pure, but from its chromatographic properties it appears to be identical with an acid obtained from xylose but different from the acid of R_L 0·51 obtained from 2-hydroxyglucal.

TABLE 4. *Degradation of monosaccharides by alkali at 25°.*

Alkali	Alkali/glucose (equiv./mole)	Salt added	Ionic strength	Total acid (equiv./mole)
		Glucose		
$Ca(OH)_2$				
Suspension	—	—	*	1·5
0·046	2·2	—	*	1·6
0·025	2·3	—	*	1·8
0·013	2·3	—	*	2·2
0·013	1·0	—	*	2·0
0·013	3·5	—	*	2·1
		$CaCl_2$		
0·013	—	0·014M	*	2·0
0·015	—	0·042M	*	2·0
0·025	—	0·024M	*	1·8
$Ba(OH)_2$				
0·044	—	—	*	1·7
0·020	—	—	*	2·6; 2·4
NaOH				
0·039	—	—	0·039	1·7
0·015	—	—	0·015	2·5; 2·3
		NaCl		
0·015	—	0·029M	0·044	2·6
0·015	—	0·076M	0·091	2·3
		$NaClO_4$		
0·015	—	0·035M	0·050	2·3
		$CaCl_2$		
0·045	—	0·022M	*	1·7
		Fructose		
$Ca(OH)_2$				
0·045	—	—	*	1·7
0·013	—	—	*	2·1
		Galactose		
0·047	—	—	*	1·5
0·038	—	—	*	1·6
0·011	—	—	*	1·8
0·009	—	—	*	2·1
		Xylose		
Suspension	—	—	*	1·4
0·010	—	—	*	1·8

* Not calculated.

TABLE 5. *Acidic products from the alkaline degradation of glucose at 25°.*

	0·01N-$Ca(OH)_2$	Equiv./mole Satd. $Ca(OH)_2$	0·05N-NaOH
Total	2·0	1·6	1·6
Formic	0·58	0·10	0·18
Other volatile acids	0·24	0·10	0·18
Lactic	0·38	0·54	0·46
Unknown acid R_L 0·48	0·18	<0·01	0·03
Glycollic + acid of R_L 0·65	0·10	0·10	0·08
Dihydroxybutyric	0·10	0·13	0·08
Lactones, R_L 0—0·3	0·04	0·14	0·06
Lactone, R_L 0·43	0·02	0·03	0·08
D-Glucometasaccharinolactone	0·16	0·11	0·19
D-Glucoisosaccharinolactone	0·04	0·08	0·05
Lactone R_L 0·65	0·08	0·10	0·08
D-Glucosaccharinolactone	0·04	0·16	0·06

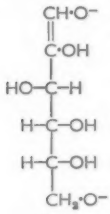
The most significant feature of Table 5 is the increase in the yield of formic acid in the case of dilute alkali. This is the main cause of the increase in yield of total acid. Recently, it has been shown that in sodium hydroxide solution, 3-dehydro-4-deoxy-D-fructose, an intermediate in the degradation of 4-substituted hexoses, undergoes fragmentation to give 0·83 equiv. of formic acid per equivalent of glucoisosaccharinic acid:[8] this does not explain the difference in yield of volatile acid from glucose in saturated and 0·01N-lime-water because of the very low yield of isosaccharinic acid (Table 5). Therefore, formic acid must

[8] Machell and Richards, *J.*, 1960, 1932.

also be produced by a reaction of unknown nature which is inversely dependent upon hydroxyl-ion concentration. Since the yield of 6-carbon saccharinic acids is high, a large percentage of the glucose must be degraded to 1 equiv. of acid per mole. This means that the yield of >2 equiv. of total acid per mole can be accounted for only by reactions producing 3 or more equiv. of acid. These reactions must involve extensive oxidation–reduction, since the systems studied were oxygen-free.

The effect of alkali on the nature of the saccharinic acids has also been determined. From paper chromatography (Table 5) it is apparent that the composition of lactonisable acids produced from glucose by 0·01N-lime-water and 0·05N-sodium hydroxide is approximately the same and that the major acid is glucometasaccharinic acid. With saturated lime-water, however, glucosaccharinic acid becomes of considerable importance, and its yield is comparable with that of glucometasaccharinic acid.

It is generally believed that the predominant saccharinic acid produced by the action of sodium hydroxide on glucose is glucometasaccharinic acid whereas that from calcium hydroxide is glucosaccharinic acid.[9] The evidence now presented suggests that glucometasaccharinic acid is a major product in both cases, as would be expected from the β-hydroxycarbonyl mechanism of the formation of saccharinic acids. However, when the calcium-ion concentration becomes appreciable, glucosaccharinic acid is formed by a different mechanism involving fragmentation and recombination.[10] This necessitates revising the explan-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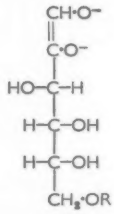
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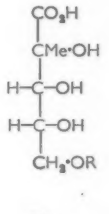
(V)

ation of the formation of 6-*O*-substituted glucometasaccharinic acids by the action of lime-water upon melibiose[11] and 6-*O*-methylglucose.[12] It was believed that because substitution of the primary hydroxyl group prevents formation of the ion (III), which leads to saccharinic acid, the ion (IV) is formed, giving rise to a metasaccharinic acid. In the light of the present work it is unnecessary to postulate the formation of doubly charged ions since the main saccharinic acid expected from a 6-*O*-substituted glucose is of the meta-type. Moreover, substitution of the primary hydroxyl group would be likely to prevent the formation of a 5-*O*-substituted saccharinic acid (V) by a fragmentation-recombination process.

Experimental

Qualitative Paper Chromatography.—Separations were made on Whatman No. 1 filter paper, development being with solvent (*a*) ethyl acetate–acetic acid–water (10 : 1·3 : 1) or (*b*) ethyl acetate–pyridine–water (8 : 2 : 1). Components were detected by the sprays (*a*) B.D.H. "4·5" indicator,[13] (*b*) sodium periodate–permanganate,[14] and (*c*) hydroxylamine–ferric chloride.[15]

Degradation of Cellobiose with Saturated Lime-water.—The degradation of cellobiose (4·748 g.)

[9] Sowden, *Adv. Carbohydrate Chem.*, 1957, **12**, 75.
[10] Sowden, Blair, and Kuenne, *J. Amer. Chem. Soc.*, 1957, **79**, 6450.
[11] Corbett and Kenner, *J.*, 1954, 3281.
[12] Kenner and Richards, *J.*, 1956, 2916.
[13] Nair and Muthe, *Naturwiss.*, 1956, **43**, 106.
[14] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.
[15] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

XUM

in saturated, oxygen-free lime-water (500 ml.) at 25° was followed as described by Corbett and Kenner [1] except that the following method was used for estimation of acids by the resin method. Aliquot portions (10 ml.) were stirred with Amberlite resin IR-120(H) (1 ml.) and phenolphthalein (1 drop) until the colour was discharged, and then for a further 10 min. The solution was filtered and the resin washed with water (5 × 5 ml.). The combined filtrate and washings were titrated with 0·01N-sodium hydroxide. A blank estimation was necessary. Results are given in Table 1. When a solution of calcium α-isosaccharinate was similarly treated, it was shown that the extent of lactone formation was less than 2·5%.

Alkaline degradation of Various Glucose Acetates.—The acetates (*ca.* 0·8 g.) were shaken in oxygen-free alkali (250 ml.) until dissolution had been attained. Samples (25 ml.) were removed periodically, acidified with 0·01N-sulphuric acid, and back-titrated with 0·05N-sodium hydroxide. Further samples, after being stirred with Amberlite resin IR-120(H), were concentrated under reduced pressure and chromatographed in solvent *a*. Sprays *a*, *b*, and *c* revealed that during the first stages of reaction of penta-*O*-acetyl-α- and -β-D-glucose with lime-water the main acidic product had R_L 0·31. It reacted instantaneously with spray *b* and with potassium permanganate alone. Slow-moving components (R_L 0·02—0·14) and traces of metasaccharinolactone (R_L 0·51) were also detected. Only slow-moving components and metasaccharinolactone were detected amongst the initial degradation products of penta-*O*-acetyl*aldehydo*- and 2,3,4,6-tetra-*O*-acetyl-D-glucose with lime-water and penta-*O*-acetyl-D-glucose with 0·045N- and 1·0N-sodium hydroxide. Quantitative results are given in Fig. 1 and 2.

Neutral Products from the Alkaline Degradation of Penta-O-*acetyl*-D-*glucose*, D-*Glucose, and Lactose.*—The sugar (50 g.) was shaken for 18 hr. with a suspension of calcium hydroxide (10 g.) in water (1 l.), and then the suspension was saturated with carbon dioxide, boiled, filtered, and concentrated under reduced pressure to a syrup. This was dissolved in a saturated solution (300 ml.) of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid and kept at room temperature for 7 days. The precipitate was centrifuged off, washed with water until free from acid, and dried. It was fractionally crystallised from ethanol, chloroform, and acetone to give from penta-*O*-acetyl-D-glucose compound A, m. p. 242—244° [Found: C, 41·2; H, 3·2; N, 21·2%; *M* (Rast) 522], and from lactose compound B, m. p. 214—219° (Found: C, 41·2; H, 3·2%). D-Glucose gave several compounds, none of which corresponded to the above.

Alkaline Degradation of Tetra-O-*acetyl*-2-*hydroxy*-D-*glucal.*—(a) *Rate of degradation.* Samples of the acetate were degraded with 0·009N- and 0·044N- and a suspension of calcium hydroxide under conditions similar to those described for the glucose acetates. In the last two experiments, an intense yellow colour was produced within 15 min. and disappeared in 0·5—1·5 hr. Results are given in Table 2.

(b) *Quantitative analysis of acid products.* (i) By 0·011N-lime-water. 2-Hydroxy-D-glucal tetra-acetate (0·649 g.) was treated with the alkali (1·2 l.) for 20 hr. at room temperature. The solution was stirred with excess of Amberlite resin IR-120(H) until free from calcium ions, and then diluted to 1·5 l. Samples (10 ml.) required 1·38 ml. of 0·05N-sodium hydroxide for neutralisation to phenolphthalein. Addition of further 0·05N-sodium hydroxide (3 ml.) followed by back-titration after 1 hr. indicated the absence of lactones. The yield of acid was therefore 5·26 equiv. per mole. The solution (1·460 l.) was concentrated under reduced pressure, and samples (10 ml.) of the distillate required 1·10 ml. of 0·05N-sodium hydroxide for neutralisation (*i.e.*, 3·97 equiv. per mole, 99·3% of theory for acetic acid). Samples of the residue were quantitatively analysed by the method described for glucose below; the results are given in Table 3.

(ii) By a suspension of lime. The acetate (0·592 g.) was similarly treated with a suspension of calcium hydroxide (5 g.) in water (1·2 l.). After 20 hr. the suspension was filtered, freed from calcium ions, and diluted to 1·5 l. Samples (10 ml.) required 1·21 ml. of 0·05N-sodium hydroxide for neutralisation. Addition of further 0·05N-sodium hydroxide (3 ml.) followed by back-titration indicated the absence of lactones. The yield of acid was therefore 5·07 equiv. per mole. The solution (1·470 ml.) was concentrated under reduced pressure and samples (10 ml.) of the distillate (1·450 l.) required 0·96 ml. of 0·05N-sodium hydroxide for neutralisation (*i.e.* 4·04 equiv. per mole, 101% for acetic acid). Samples of the residue were quantitatively analysed as above; results are given in Table 3.

Alkaline degradation of Various Monoses: Acid Yields.—The initial ratio of alkali to monose was, as far as possible, 2·3 equiv. per mole. At intervals aliquot portions of the reaction mixture were removed for analysis. Acid production was estimated by back-titration, except for the

XUM

experiments with a suspension of lime where the resin method as described for the cellobiose experiments was used. Monose consumption was measured by the fall in reducing power towards potassium ferricyanide.[16] Results are given in Table 4.

Lobry de Bruyn–Alberda van Ekenstein Transformation of Glucose.—Solutions of D-glucose (4·5 g.) in oxygen-free saturated lime-water (25 ml.) and in 0·04N-sodium hydroxide (25 ml.) were kept at 25° until their optical rotations were constant (500—800 hr.). After treatment with excess of Amberlite resin IR-120(H), the solutions were submitted to quantitative paper chromatography with solvent *b*. By this method the mixture was separated into only two bands, the slower being glucose and the faster fructose plus mannose. Total sugars in each band were estimated by Hagedorn and Jensen's method,[16] and fructose in the faster fraction by Bell's method.[17] In both cases the equilibrium mixture contained glucose 66%, fructose 33%, and mannose 1%.

Alkaline degradation of Glucose: Analysis of Acidic Products.—The acidic degradation products of glucose from 0·05N-sodium hydroxide and 0·01N- and a suspension of calcium hydroxide were determined by the same method. Details for the experiment with 0·05N-sodium hydroxide are given as an example. Glucose (4·026 g.) in oxygen-free alkali (1 l.) was kept at 25° until *ca.* 80% degradation had occurred.

(a) *Volatile acids.* Aliquot portions (100 ml.) of the reaction mixtures were stirred with Amberlite resin IR-120(H) (10 ml.) for 20 min., then filtered, and washed with water (5 × 10 ml.). The combined filtrate and washings were evaporated and the volatile acids determined by Richards and Sephton's method.[18] Formic acid was oxidised by refluxing a sample of the volatile acids with an excess of mercuric oxide for 2·5 hr., the residual acidity being determined by titration to thymolphthalein.

(b) *Non-volatile acids.* An aliquot portion (400 ml.) of the reaction mixture was stirred with Amberlite resin IR-120(H) (70 ml.) for 2 hr., then filtered, and the resin was washed with water (4 × 50 ml.). The combined filtrate and washings were concentrated to a solution containing 0·104 milliequiv. of acid plus lactone per ml. Samples (10 ml.) were chromatographed on Whatman No. 3MM paper (12 in. wide) in solvent *a*. After the solvent had been allowed to evaporate (steaming was necessary in dry atmospheres), guide strips were sprayed with spray *a* to locate the position of the acids. The entire chromatograms were then cut into strips, and the acids and lactones were eluted with water (75—100 ml.). The acidity of the eluants was determined by direct titration. Further 0·01N-sodium hydroxide (2 ml.) was added and the solution kept for 1 hr. in an atmosphere of nitrogen. The lactone concentration was determined from the excess of alkali. Determinations were made in triplicate.

(c) *Lactonisable acids.* An aliquot portion (20 ml.) of the concentrated solutions used for the above analyses was diluted to 30 ml., stirred with Amberlite resin IRA-400 (CO_3) (1·5 ml.) until it was of pH 4·0, and then filtered. The resin was washed with water (4 × 10 ml.) and the combined filtrate and washings were diluted to 100 ml. Titration of duplicate samples (5 ml.) indicated that the lactones were recovered in 96% yield whereas 95·5% of the acids were removed. The remaining solution was concentrated (to *ca.* 5 ml.) and chromatographed on Whatman No. 3MM paper as described above except that the lactones on the guide strips were detected by spray *c*. Estimations were duplicated.

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WYTHENSHAWE, MANCHESTER, 22. [*Received, July 8th*, 1960.]

[16] Hagedorn and Jensen, *Biochem. Z.*, 1923, **135**, 46.
[17] Bell, "Modern Methods of Plant Analysis," Springer-Verlag, Berlin, 1955, Vol. II, p. 21.
[18] Richards and Sephton, *J.*, 1957, 4492.

106. *The Preparation of the Geraniolenes.*

By M. F. Ansell and D. A. Thomas.

The Wittig reaction has been utilised in the synthesis of the geraniolenes, (2,6-dimethylhepta-1,5-, -2,5-, and -1,6-diene). Syntheses of 2-methylhex-1- and -2-ene are reported.

Thermal decarboxylation of geranic acid (I) to geraniolene (III) was reported by Tiemann and Semmler [1] in 1893. This formulation of geraniolene and its precursor was shown, by Bateman, Cuneen and Waight [2] in 1952, to be essentially correct, although in the intervening period [3] the alternative structure (II) had been proposed for geranic acid, and structures (IV) and (V) for geraniolene. Of these isomeric geraniolenes, 2,6-dimethylhepta-1,5-diene (III) has been obtained [4] by coupling of 1-methylallyl chloride and 3-methylbut-2-enyl chloride in the presence of magnesium. 2,6-Dimethylhepta-1,5-diene (III)

(I) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2H$ $\quad$ $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2H$ (II)

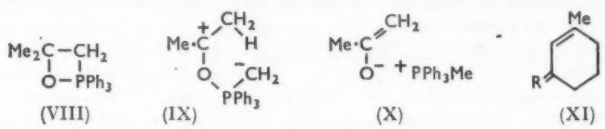
(III) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH_2$ $\quad$ $CMe_2{:}CH{\cdot}CH_2{\cdot}CH{:}CMe_2$ (IV)

$CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH_2$ (V) $\quad$ $R{\cdot}CH_2{\cdot}COMe$ (VI) $\quad$ $R{\cdot}CH{:}PPh_3$ (VII)

R = (a) Pr^n, (b) $CMe_2{:}CH{\cdot}CH_2$, (c) $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2$

and the 2,5-diene (IV) have been obtained [2] by fractioning the dehydrochlorination product from 6-chloro-2,6-dimethylhept-2-ene. 2,6-Dimethylhepta-1,6-diene (V) has not previously been reported. Utilisation of the authentic isopropenyl and isopropylidene intermediates previously reported,[5,6] and application of the Wittig reaction,[7] have led to unambiguous syntheses of the three geraniolenes.

At the outset of our work, use of the Wittig reaction for synthesis of simple aliphatic isopropenyl and isopropylidene isomers had not been reported, although cholest-24- and -25-ene had been obtained [8] by this reaction. Its applicability was shown by the preparation of 2-methylhex-1-ene from hexan-2-one (VIa) and methylenetriphenylphosphorane and of 2-methylhex-2-ene from acetone and the butylidenephosphorane (VIIa). It has since been used in the preparation of 2-methylnon-1-ene by Oliver, Smith, and Fenning [9] who discuss the preparation of some isopropylidene and isopropenyl isomers.



(VIII) (IX) (X) (XI)

2,6-Dimethylhepta-1,5-diene (III) was obtained in low yield by the action of methylenetriphenylphosphorane on 6-methylhept-5-en-2-one (VIb) as well as by that of the phosphorane (VIIc) on acetone. In the latter reaction mesityl oxide was also formed. This is the first example of a Wittig reagent catalysing a condensation of aldol type. This is explicable if the first step is the formation of the intermediate (IX) which may then be converted either into the Wittig intermediate (VIII) or by abstraction of a proton from

[1] Tiemann and Semmler, *Ber.*, 1893, **26**, 2724.
[2] Bateman, Cuneen, and Waight, *J.*, 1952, 1714.
[3] Simonsen, "The Terpenes," Vol. I, Cambridge Univ. Press, 1947, p. 7.
[4] Henne and Chanan, *J. Amer. Chem. Soc.*, 1944, **66**, 392.
[5] Ansell and Brown, *J.*, 1957, 1788.
[6] Ansell and Thomas, *J.*, 1958, 1163.
[7] Schollkopf, *Angew. Chem.*, 1959, **71**, 260.
[8] Fagerland and Idler, *J. Amer. Chem. Soc.*, 1957, **79**, 6473; Bergmann and Dusza, *J. Org. Chem.* 1958, **23**, 459.
[9] Oliver, Smith, and Fenning, *Chem. and Ind.*, 1959, 1575.

XUM

the α-methylene position of the ketone into the enolate ion (X) which may then condense with another molecule of acetone.

2,6-Dimethylhepta-2,5-diene (IV) was obtained, in low yield, together with mesityl oxide, by interaction of 4-methylpent-3-enylenetriphenylphosphorane (VIIb) and acetone. An attempt to prepare this diene from acetone and the Wittig reagent derived from 1,3-trimethylenebistriphenylphosphonium dibromide was unsuccessful, only mesityl oxide being obtained.

The previously unknown 2,6-dimethylhepta-1,6-diene (V) was obtained from 6-methylhept-6-en-one (VIIc) and methylenetriphenylphosphorane. An alternative route to this diene, the action of methylenetriphenylphosphorane on heptane-2,6-dione, yielded a hydrocarbon product which from its infrared spectrum contained a terminal methylene group, and from its ultraviolet spectrum ($\lambda_{max.}$ 237 mμ) contained a conjugated diene system. These data are not consistent with either of the possible acyclic conjugated dienes, both of which are known.[2] However, heptane-2,6-dione is known [10] to cyclise readily to 3-methylcyclohex-2-enone (XI; R = O) (cf. formation of mesityl oxide above), and this could then react with methylenetriphenylphosphorane to yield 1-methyl-3-methylenecyclohex-1-ene (XI; R = CH_2). From Woodward's rules [11] this compound would exhibit absorption at 237 mμ. It is considered that the product of this reaction is a mixture of the dienes (V) and (XI; R = CH_2).

The various methyl ketones used in this work had been previously reported (see Experimental section), and it was found that they could be conveniently prepared by the action of the appropriate Grignard reagent on acetic anhydride at −70°, a method described by Newman and Booth.[12]

Experimental

Refractive indices are for the Na_D line at 20° unless otherwise stated. Fractional distillations marked (S) were effected with a spinning-band semimicrofractionating column (E. Haage, Mulheim). All isopropenyl compounds showed absorption in the region 11·24—11·36 and 6·02—6·06 μ, and all isopropylidene compounds in the region 12·05—12·20 and 5·95—5·99 μ.

5-Iodo-2-methylpent-1-ene.—4-Methylpent-4-en-1-ol [6] (35 g.) was added during 1 hr. to a stirred slurry of toluene-*p*-sulphonyl chloride (73·5 g.) in pyridine (38 ml.) at 20° ± 2°. After a further hour's stirring at room temperature the mixture was cooled to 0° and water (25 ml.) added with stirring. The mixture was poured into an equal volume of ice-water, extracted with ether, washed with ice-cold 25% sulphuric acid, saturated sodium hydrogen carbonate solution, and water, and dried (K_2CO_3). Evaporation (finally at 50°/1 mm.) gave *4-methylpent-4-en-1-yl toluene*-p-*sulphonate* (69 g., 77%), *n* 1·5101—1·5110 (Found: C, 61·6; H, 7·0; S, 12·7. $C_{13}H_{18}O_3S$ requires C, 61·2; H, 7·2; S, 12·6%). This was stirred with sodium iodide (45 g.) in acetone (250 ml.) under reflux for 2 hr. After being cooled to 0°, the precipitated sodium toluene-*p*-sulphonate was filtered off and washed with ether, and the solvents were evaporated. The residue was washed with excess of 10% sodium thiosulphate solution, and water, dried ($MgSO_4$), and distilled, to yield *5-iodo-2-methylpent-1-ene* (40 g., 69%), b. p. 60—63°/16 mm., *n* 1·5105. A redistilled (S) sample had b. p. 62°/17 mm., *n* 1·5144 (Found: C, 34·5; H, 5·6; I, 60·9. $C_6H_{11}I$ requires C, 34·3; H, 5·3; I, 60·4%). The derived *thiouronium picrate* (yellow laths from ethanol) had m. p. 148·5—149·5° (Found: C, 40·55; H, 4·7; N, 17·8. $C_{13}H_{17}N_5O_7S$ requires C, 40·3; H, 4·4; N, 18·1%); *5-methyl-N-1-naphthylhex-5-enamide* (prepared *via* the Grignard reagent) formed needles (from alcohol), m. p. 133° (Found: C, 80·5; H, 7·5; N, 5·6. $C_{17}H_{19}NO$ requires C, 80·6; H, 7·6; N, 5·5%).

6-Methylhept-5-en-2-one.—A solution of the Grignard reagent from 5-iodo-2-methylpent-2-ene [5] (30·6 g., 0·15 mole) and magnesium (3·6 g.) in ether (150 ml.) was added during 1 hr. to a solution of acetic anhydride (15·3 g.) in ether (20 ml.) stirred at −60°. After being stirred at −60° for 1 hr. the mixture was allowed to warm to room temperature, then poured on ice and ammonium chloride, the aqueous layer was separated and extracted with ether, and the

[10] Fargher and Perkin, *J.*, 1914, 1353.
[11] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.
[12] Newman and Booth, *J. Amer. Chem. Soc.*, 1945, **67**, 154.

combined extracts were washed with 2N-sodium hydroxide (2 × 50 ml.) and water (100 ml.), dried ($MgSO_4$), and distilled to yield 6-methylhept-5-en-2-one (9·5 g., 50%), b. p. 62—66°/15 mm., n 1·4400. A redistilled (S) sample had b. p. 62°/17 mm., n 1·4387 (lit.,[13] b. p. 58—59°/10 mm., n^{25} 1·4372).

6-Methylhept-6-en-2-one.—This ketone was prepared as in the previous experiment, from 5-iodo-2-methylpent-1-ene in 63% yield and had b. p. (S) 59°/15 mm., n 1·4333. Albisetti *et al.*[14] record b. p. 170—172°, n_D^{25} 1·4358; Kappeler *et al.*[15] record b. p. 53—57°/11 mm., n^{19} 1·4344. The m. p.s of the derived semicarbazone and 2,4-dinitrophenylhydrazone agree with those reported.

Hexan-2-one.—This ketone was prepared, as for 6-methyl-hept-5-en-2-one, from butylmagnesium bromide and acetic anhydride in 66% yield and had b. p. 126—127°, n 1·4002 (lit.,[16] b. p. 126°, n 1·4001).

n-Butyltriphenylphosphonium Bromide.—A solution of n-butyl bromide (34·2 g.) and triphenylphosphine (59 g.) in dry nitromethane (225 ml.) was boiled for 16 hr. The solvent was removed at ~15 mm. and the residual crystals were washed with dry benzene (4 × 100 ml.) and dried in a high vacuum, to yield n-butyltriphenylphosphonium bromide (71·5 g., 79%), m. p. 241—243° (lit.,[17] 223°) (Found: Br^-, 19·3. Calc. for $C_{22}H_{24}PBr$: Br^-, 20·0%).

4-Methylpent-3-enyltriphenylphosphonium Iodide.—A solution of 5-iodo-2-methylpent-2-ene [5] (67 g.) and triphenylphosphine (78·6 g.) in dry benzene (200 ml.) was boiled for 3 hr., during which two layers separated. On being cooled the lower layer crystallised; the upper layer was decanted and evaporated to yield more of the salt. The solid fractions were combined, washed with dry ether, and dried in a high vacuum, to yield *4-methylpent-3-enylphosphonium iodide* (125 g., 88%), white prisms, m. p. 142° (Found: C, 61·0; H, 5·30; I, 26·55. $C_{24}H_{26}IP$ requires C, 61·0; H, 5·50; I, 26·9%).

4-Methylpent-4-enyltriphenylphosphonium Iodide.—This *phosphonium salt* (white prisms, m. p. 161°) was prepared (89%) from 5-iodo-2-methylpent-1-ene as in the previous experiment (Found: C, 61·4; H, 5·4; I, 26·55%).

General Procedure for Wittig Reactions.—A suspension of the finely powdered phosphonium salt (0·2 mole) in dry ether (1 l.) was stirred under nitrogen, and a solution of phenyl-lithium (0·2 mole) in ether (*ca.* 200 ml.) was added during 30 min. The mixture was stirred and boiled for 2 hr. while ether (850 ml.) was removed by distillation. A solution of the ketone (0·2 mole)

No.	RPh_3PX: R	X	Ketone	Product
1	Me	Br	Bu^n·COMe	Bu^n·CMe:CH_2
2	Bu^n	Br	$COMe_2$	Pr^n·CH:CMe_2
3	CMe_2:CH·$[CH_2]_2$	I	$COMe_2$	CMe_2:CH·CH_2·CH:CMe_2 [a]
4	CH_2:CMe·$[CH_2]_2$	I	$COMe_2$	CMe_2:CH·CH_2·CH_2·CMe:CH_2
5	Me	Br	CMe_2:CH·$[CH_2]_2$·COMe	" "
6	Me	Br	CH_2:CMe·$[CH_2]_2$·COMe	CH_2:CMe·$[CH_2]_2$·CMe:CH_2 [b]
7	Me	Br	Me·CO·$[CH_2]_2$·COMe	{ (XI; R = CH_2) "

No.	Yield (%)	B. p. Found	B. p. Lit.	n_D^{20} Found	n_D^{20} Lit.
1	11·5	90—91°	91·8° [d]	1·4037	1·4035 [d]
2	20	91—92	95·1,[e] 94—94·5	1·4071	1·4080,[e] 1·4070
3	14·5	149	150—151	1·4457	1·4490 [f]
4	11·5	139	141—142 [g]	1·4391	1·4388 [g]
5	10	139	"	1·4385	"
6	10·5	138—139	—	1·4363	—
7	6·5	137—139	—	1·4373	—

[a] Also mesityl oxide. [b] 2,6-*Dimethylhepta*-1,6-*diene* (Found: C, 86·9; H, 12·8. C_9H_{16} requires C, 87·1; H, 12·9%). [c] Found: C, 87·7; H, 12·4%. [d] Schumacher, Wibaut, and Parels, *Rec. Trav. chim.*, 1953, **72**, 1037. [e] n_D^{25}; Sutherland, *J. Amer. Chem. Soc.*, 1953, **75**, 5949. [f] Nesmeyanov, Friedlina, and Kochetkov, *Bull. Acad. Sci. U.S.S.R.*, 1951, 273. [g] Ref. 2.

[13] Kimel, Sax, Kaiser, Eichmann, Chase, and Ofner, *J. Org. Chem.*, 1958, **23**, 153.
[14] Albisetti, Fisher, Hogsed, and Joyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2637.
[15] Kappeler, Stauffacher, Eschenmoser, and Schinz, *Helv. Chim. Acta*, 1954, **37**, 957.
[16] Percival, Wagner, and Cook, *J. Amer. Chem. Soc.*, 1953, **75**, 3731.
[17] Friedrich and Henning, *Chem. Ber.*, 1959, **92**, 2756.

XUM

in ether (20 ml.) was then added slowly and the mixture heated at 60—75° for 4 hr. The cold mixture was then filtered into a cooled (−60°) receiver and the residue washed with ether. The filtrate was then distilled at reduced pressure (well-cooled receivers), the distillate fractionated through a small column to remove ether, and the residue fractionated (S). The products are tabulated.

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QUEEN MARY COLLEGE, LONDON, E.1. [*Received, July* **13***th*, 1960.]

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107. *Aromatic Reactivity. Part XIV.*[1] *Cleavage of Aryltricyclohexyl- and Aryltrimethyl-stannanes by Aqueous-ethanolic Perchloric Acid.*

By C. EABORN and J. A. WATERS.

We have measured the rates of cleavage of some tricyclohexyl- and trimethyl-phenylstannanes and of *p*-methoxyphenyltriphenylstannane by a mixture of ethanol (50 vol.) and aqueous perchloric acid (2 vol.) at 50·0°. As expected for an electrophilic aromatic substitution, electron-releasing substituents in the phenyl group increase the ease of cleavage and electron-withdrawing substituents decrease it (the *p*-methoxy- and *p*-trimethylammonio-derivative are 63 and 0·0068 times, respectively, as reactive as tricyclohexylphenylstannane). The $+E$ effects of substituents appear to operate less effectively in this reaction than in most electrophilic aromatic substitutions, including the analogous cleavages of aryl-silicon and aryl-germanium bonds.

IT has been shown that cleavages of Ar–Si and Ar–Ge bonds by electrophilic reagents are electrophilic aromatic substitutions, analogous to those in which Ar–H bonds are broken, and that the effects of substituents in the aryl groups can be correlated with those in more familiar electrophilic aromatic substitutions such as nitration, halogenation, or hydrogen-exchange.[2-7] Electrophilic reagents, such as acids, halogens, and mercuric, silver, or thallium salts, cleave Ar–Sn bonds even more readily than Ar–Si and Ar–Ge bonds, and we now report a kinetic study of the cleavage at 50·0° of substituted tricyclohexylphenylstannanes by a mixture of ethanol (50 vol.) and aqueous perchloric acid (2 vol.):

$$(C_6H_{11})_3Sn{\cdot}C_6H_4{\cdot}X + MOH \xrightarrow{H^+} (C_6H_{11})_3Sn{\cdot}OM + C_6H_5{\cdot}X \ (M = Et \text{ or } H)$$

$$(C_6H_{11})_3Sn{\cdot}OM + HClO_4 \rightleftharpoons (C_6H_{11})_3SnClO_4 + MOH$$

The reactions were studied spectrophotometrically.

We chose tricyclohexyl compounds for the main study because, being solids, they could be purified by recrystallization, but their relative insolubility in the aqueous-methanolic mixtures used for silicon and germanium compounds[3,6] caused us to use ethanol containing only a little water. We examined *p*-methoxyphenyltriphenylstannane and a few trimethylphenylstannanes for comparison with the tricyclohexyl compounds.

The results for the tricyclohexylphenylstannanes are shown in Table 1. Observed first-order rate constants, k, are listed, along with the rate, k_{rel} for each compound relative

[1] Part XIII, Eaborn and Taylor, *J.*, 1961, 247.
[2] Eaborn, "Organosilicon Compounds," Butterworths Sci. Publ., London, 1960, pp. 146—156.
[3] Eaborn, *J.*, 1956, 4858.
[4] Eaborn and Webster, *J.*, 1957, 4449; 1960, 179.
[5] Deans and Eaborn, *J.*, 1959, 2299.
[6] Eaborn and Pande, *J.*, 1961, 297.
[7] Benkeser, Hoke, and Hickner, *J. Amer. Chem. Soc.*, 1958, **80**, 5294.

XUM

to that of the unsubstituted compound, tricyclohexylphenylstannane. The rates were not all measured at the same acid concentration (and thus the same ethanol–water ratio), and the values of k_{rel} are derived by the overlap procedure previously used.[3,5,6] Slightly different values might be obtained for some of the compounds if all were measured directly in, say, the medium containing 0·6M(added)-perchloric acid. It will be noticed that at the lowest acid concentrations the rate increases only a little faster than the concentration of acid, but rises more steeply at higher concentrations, behaviour which seems to be normal for acid-catalysed reactions in alcohols or in aqueous alcohols of low water content.[8]

Derivation of the value of k_{rel} for the *p*-dimethylamino-compound requires explanation. The fact that the rate of cleavage for this compound is doubled by doubling the acid concentration indicates that it is mainly present as the free base at the acid concentrations used. (Spectrophotometric measurements show this to be true for dimethylaniline, which probably has a comparable base strength.) If a substantial proportion of the compound were present as the unreactive protonated base, then additional protonation would counteract the normal increase in rate associated with increase in acid concentration. (For a discussion of the behaviour of an analogous silicon compound see ref. 3.) If proportionality between rate and acid concentration is assumed for the *p*-methoxy-compound at the low acid concentrations involved, then k for this compound would be 0·62 min.$^{-1}$ for 0·0020M(added)-acid, and thus k_{rel} for the *p*-dimethylamino-compound would be 63(161/0·62), *i.e.*, $1·6 \times 10^4$. Since, in fact, the rate for the *p*-methoxy-compound probably falls off somewhat more steeply than the acid concentration, the figure of 2×10^4 which we assign to k_{rel} for the *p*-dimethylamino-compound in Table 1 may be slightly low, but it is probably within 50% of the correct value.

TABLE 1. *Cleavage of* $X{\cdot}C_6H_4{\cdot}Sn(C_6H_{11})_3$ *compounds at* 50·0°.

X	$[HClO_4]$ [a] (M)	10^3k (min.$^{-1}$)	k_{rel}	X	$[HClO_4]$ [a] (M)	10^3k (min.$^{-1}$)	k_{rel}
p-NMe_2	0·0010	77	—	*p*-Ph	0·571	6·24	1·77
	0·0020	161	*ca.* 2×10^4	H	0·099	0·54	
p-MeO	0·0283	8·75	—		0·571	3·53	
	0·099	34·0	63		2·35	17·8	1
p-Bu^t	0·313	12·6	—		3·41	29·2	
	0·571	24·4	6·9		4·48	46·0	
	2·35	128	7·2	*m*-MeO	2·35	15·9	0·89
p-Pr^i	0·313	12·2	—		4·48	37·8	0·82
	0·571	24·0	6·9	*p*-F	4·48	28·5	0·62
	2·35	124	7·0	*p*-Cl	4·48	8·63	0·187
p-Et	0·313	10·2	—	*p*-Br	4·48	6·68	0·145
	2·35	94	5·3	*m*-Cl	4·48	1·78	0·039
p-Me	0·099	2·97	5·5		9·15	5·92	—
	0·313	10·4	—	*p*-CO_2H	9·15	4·60	0·030
	0·571	20·4	5·8	*p*-NMe_3^+ [b]	9·15	1·04	0·0068
	2·35	95·5	5·4				
m-Me	0·571	6·49	1·84				
	2·35	33·0	1·85				
o-Ph	0·571	7·02	1·99				

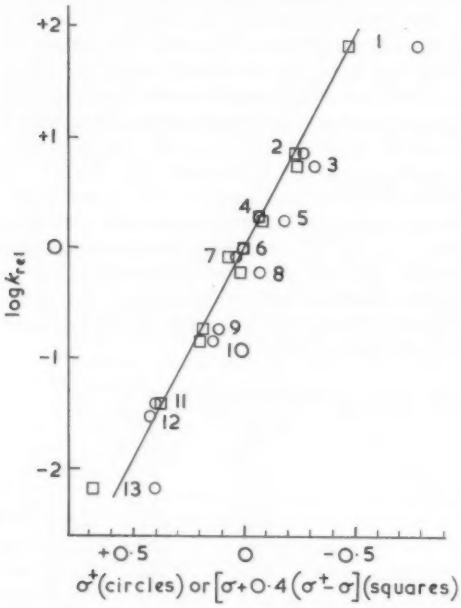
[a] Concn. of aqueous acid, 2 vol. of which was mixed with 50 vol. of an ethanolic solution of the organostannane. [b] The methiodide of *p*-dimethylaminophenyltricyclohexylstannane was used.

Comparison of the values of k_{rel} for destannylation of the $(C_6H_{11})_3Sn{\cdot}C_6H_4{\cdot}X$ compounds with those which apply in desilylation of $Me_3Si{\cdot}C_6H_4{\cdot}X$ compounds,[3] and degermylation of $Et_3Ge{\cdot}C_6H_4{\cdot}X$ compounds,[6] both in aqueous methanol, reveals that, while the substituents lie in much the same order with respect to their activating or deactivating effects, there are differences in detail. The most striking difference is in the overall spread of rates; thus the *p*-methoxy-group, which activates 1500 and 540 times, respectively, in desilylation and degermylation, activates only 63 times in the destannylation,

[8] Long and Paul, *Chem. Rev.*, 1957, **57**, 935; Satchell, *J.*, 1957, 2878; Baines and Eaborn, *J.*, 1956, 1436.

XUM

while the *m*-chloro-atom deactivates 26 times, compared with 60 times in degermylation. A linear free-energy relation, such as applies between the substituent effects in desilylation and degermylation,[6] does not apply between the effects in either of these reactions and those in destannylation. Neither is a straight line obtained when log k_{rel}^{Sn} (the superscript denotes which demetallation is involved) is plotted against the electrophilic substituent constants, σ^+,[9] which apply approximately to degermylation and desilylation, as to a wide variety of electrophilic aromatic substitutions and related reactions (see Figure). A plot of log k_{rel}^{Sn} against the Hammett substituent constant, σ,[10] is also unsatisfactory.



Relations between substituent constants and rates of cleavage of $X{\cdot}C_6H_4{\cdot}Sn(C_6H_{11})_3$ *compounds, where* X *is*: 1, *p*-MeO; 2, *p*-Bu^t; 3, *p*-Me; 4, *m*-Me; 5, *p*-Ph; 6, H; 7, *m*-MeO; 8, *p*-F; 9, *p*-Cl; 10, *p*-Br; 11, *m*-Cl; 12, *p*-CO_2H; 13, *p*-NMe_3^+.

It is rewarding to analyse the substituent effects using Yukawa and Tsuno's method.[11] As they have pointed out, the quantity $(\sigma^+ - \sigma)$ is a measure of the potential ability of a group to stabilize by resonance effects (mainly, presumably, by its $+E$ effect) a centre of excess of positive charge with which it is conjugated, and the extent to which the resonance effects operate differs from reaction to reaction. For a large number of electrophilic reactions, Yukawa and Tsuno showed that the relation $\log k_{rel} = \rho[\sigma + r(\sigma^+ - \sigma)]$ is more satisfactory than either of the relations $\log k_{rel} = \rho\sigma$ or $\log k_{rel} = \rho\sigma^+$.* By definition, $r = 1$ for solvolysis of αα-dimethylbenzyl chlorides in 90% aqueous acetone, and $r = 0$ for ionization of benzoic acids in water, and can have a range of values above zero, for example: 2·29 in brominolysis of benzeneboronic acids ($\rho = -3{\cdot}84$), 1·66 in halogenation of substituted benzenes in acetic acid ($\rho = -8{\cdot}82$), 0·897 for nitration of substituted benzenes in nitromethane or acetic acid ($\rho = -6{\cdot}38$), and 0·436 for the Beckmann rearrangement of acetophenone oximes in 94·5% sulphuric acid ($\rho = 1{\cdot}98$). It

* For a related analysis of substituent effects see ref. 12. A treatment equivalent to Yukawa and Tsuno's, but applicable to reactions in which there is a *loss* of resonance stabilization on going from initial state to transition state, has been proposed by Dickinson and Eaborn.[13]

[9] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.
[10] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420; Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[11] Yukawa and Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 971.
[12] Bekhum, Verkade, and Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.
[13] Dickinson and Eaborn, *J.*, 1959, 3036.

should be noted that from reaction to reaction, r, which measures the extent to which the "resonance potential" of the substituents is brought into play, does not necessarily increase with ρ, which measures the general demand for electrons at the reaction site.

Desilylation [3,9] and degermylation [6] give fairly good straight line log k_{rel}–σ^+ plots, but there are significant deviations from the line, and plots of log k_{rel}^{Si} against $[\sigma + 0{\cdot}7(\sigma^+ - \sigma)]$ ($\rho = 5{\cdot}0$) and of log k_{rel}^{Ge} against $[\sigma + 0{\cdot}65\ (\sigma^+ - \sigma)]$ ($\rho = 4{\cdot}6$) are distinctly better.* For destannylation, the appropriate relation is log $k_{rel}^{Sn} = 3{\cdot}8\ [\sigma + 0{\cdot}4(\sigma^+ - \sigma)]$ (see Figure). (The deviation for the p-NMe_3^+ group is not significant in view of the uncertainty of the σ constant,[9,10] but real deviation for this positively charged group in a reaction involving a positively charged electrophilic species would not be surprising.[5]) The value of ρ is quite large in destannylation, though markedly smaller than in the other two demetallations, and the relatively small effect of a p-methoxy-group is largely associated with a low value of the resonance factor, r.

The relative unimportance of the resonance effects of substituents enables us to understand several differences between the substituent effects in destannylation and those in desilylation or degermylation. Thus although the p-methoxy-group has such a small effect in destannylation, the m-chloro-atom, which operates mainly through its $-I$ effect, has a deactivating effect (26-fold) not very far removed from that in degermylation (60-fold). Again, the inductive order of activation p-$Bu^t > p$-Me applies in destannylation, while the Baker–Nathan order p-Me $> p$-Bu^t, which may reflect the greater hyperconjugative effect of the methyl group, applies in desilylation and degermylation, as in most electrophilic substitutions (the only exceptions noted previously being detritiation in some media [14] and nitration [15]).

Another substituent whose effect reflects strongly the demand on $+E$ effects is the *para*-phenyl group; [16,17] the following rate factors show how activation, f_p^{Ph}, by this group varies compared with activation, f_m^{Me}, by the m-methyl group for which $+E$ effects must be negligible: molecular chlorination, $f_p^{Ph} = 595$, $f_m^{Me} = 4{\cdot}95$; [16,18,19] ionic bromination, $f_p^{Ph} = 15{\cdot}6$, $f_m^{Me} = 2{\cdot}5$; [16] nitration, $f_p^{Ph} = 11{\cdot}0$, $f_m^{Me} = 2{\cdot}5$; [15,16] desilylation, $f_p^{Ph} = 2{\cdot}8$, $f_m^{Me} = 2{\cdot}2$; [17] degermylation, $f_p^{Ph} = 2{\cdot}69$, $f_m^{Me} = 2{\cdot}1$.[6] In destannylation the p-phenyl group actually activates to only about the same extent as the m-methyl group ($f_p^{Ph} = 1{\cdot}77$; $f_m^{Me} = 1{\cdot}84$).

TABLE 2. *Cleavage of* $X{\cdot}C_6H_4{\cdot}SnMe_3$ *compounds and of* p-$MeO{\cdot}C_6H_4{\cdot}SnPh_3$.

Compound	[Acid] (M)	10^3k (min.$^{-1}$)	k_{rel}	Compound	[Acid] (M)	10^3k (min.$^{-1}$)	k_{rel}
$C_6H_5{\cdot}SnMe_3$	2·35	90	1	p-$Cl{\cdot}C_6H_4{\cdot}SnMe_3$ ...	2·35	34·5	0·38
	0·099	3·1	1	m-$Cl{\cdot}C_6H_4{\cdot}SnMe_3$ ...	2·35	15·8	0·18
p-$Me{\cdot}C_6H_4{\cdot}SnMe_3$ ...	0·099	10·7	3·4	p-$MeO{\cdot}C_6H_4{\cdot}SnPh_3$	2·35	31·5	—

It has been suggested that the large increase in the ease of acid cleavage on going from Ar–Si and Ar–Ge bonds to Ar–Sn bonds may indicate a change of mechanism.† The fall in ρ and, more particularly, in r, may be associated with such a change in mechanism, but for the present we infer only that the electrons of the weak, highly polarizable, Ar–Sn

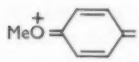
* Where r has a value in the range 0·7—1·3, log k_{rel}–σ^+ plots approximate reasonably to straight lines.[11]

† One possibility tentatively suggested by Eaborn and Pande for the mechanism of destannylation involved assumption of rapid co-ordination of a solvent molecule to the tin atom in $ArMR_3$ compounds.[20] This assumption, which was not well based and may be incorrect, is being tested.

[14] Eaborn and Taylor, *Chem. and Ind.*, 1959, 949.
[15] Cohn, Hughes, Jones, and Peeling, *Nature*, 1952, **162**, 291.
[16] de la Mare and Hassan, *J.*, 1957, 3004.
[17] Deans, Eaborn, and Webster, *J.*, 1959, 3031.
[18] de la Mare, Hall, Harris, and Hassan, *Chem. and Ind.*, 1958, 1086.
[19] Brown and Stock, *J. Amer. Chem. Soc.*, 1957, **79**, 5175.
[20] Eaborn and Pande, *J.*, 1960, 1566.

XUM

bond are probably readily available to help in the formation of the Ar–HOM bond, so that only a small excess of positive charge is concentrated on the central carbon in the highest-energy transition state, and there is only a small demand on the electrons of the ring, and particularly on the $+E$ effects of substituents. Another factor which may lead to low f values in demetallations of $Ar{\cdot}MR_3$ compounds is resonance stabilization of the initial states, involving d_π–p_π bonding of the type indicated, for example, in structure (I), for resonance effects which stabilize the transition state will be to some extent obscured by this stabilization of the initial state. It is impossible at present to decide how the importance of d_π–p_π bonding in $Ar{\cdot}MR_3$ compounds varies in the series M = Si, Ge, Sn; Chatt and Williams concluded that there was probably little change in the degree of such bonding for the three elements,[21] but this conclusion depends on assumptions about the electronegativities of the elements which may be incorrect.[6,22]



(I)

The trimethylphenylstannanes (see Table 2) are more readily cleaved than the corresponding tricyclohexyl compounds, the factor being *ca.* 5·4 for the unsubstituted compounds. The effects of substituents are smaller for the trimethyl compounds. These differences may originate in steric effects, the cyclohexyl groups not only hindering any nucleophilic attack at the tin atom, but, what is probably more important, also hindering solvation around the reaction site in the transition state. Since the excess of positive charge on the central carbon is less stabilized by solvation, not only will the tricyclohexyl compounds be less reactive but there will also be a greater demand on the electrons of the ring.

p-Methoxyphenyltriphenylstannane is about 35 times less reactive than the corresponding tricyclohexyl compound. This deactivating effect of phenyl groups attached to the metal is paralleled in cleavages of Ar–$SiPh_3$ and Ar–$GePh_3$ bonds, and presumably arises mainly from the electron-withdrawing effect of phenyl compared with alkyl groups

Failure of Linear Free-energy Relations in Electrophilic Aromatic Substitution.—We wish to stress a more general aspect of our results, *viz.*, the demonstration that the effects of substituents in an electrophilic aromatic substitution cannot necessarily be interpreted, even approximately, directly in terms of their σ^+ constants. Further, our work demonstrates that certain other observations associated with application of the analysis of substituent effects in terms of σ^+ constants do not extend to all electrophilic aromatic substitutions. For example, it was demonstrated that for those electrophilic aromatic substitutions for which accurate data were available, the ratio $(\log f_p^{Me})/(\log f_m^{Me})$ had a value in the range 3·18—4·72.[23] The value of this ratio in destannylation is 2·8, and there seems no reason why even lower values should not be found. (A value of 2·9 has been noted in detritiation.[1,14]) It has indeed been envisaged by H. C. Brown and his coworkers [24] that exceptions to their generalizations may be found for reactions which differ seriously in detailed mechanism from that accepted for the more familiar aromatic substitutions such as nitration or bromination.

Experimental

Materials.—The preparation of the organotin compounds will be described elsewhere.

Ethanol was dried [25] and fractionally distilled.

Rate Measurements.—The general procedures have been described.[3,6,20] To 50 ml. of a solution of the organotin compound in ethanol, of concentration noted in Table 3, 2 ml. of aqueous perchloric acid were added from a microburette. The rate of change of the optical density of the solution at the wavelength(s), λ, noted in the Table, was measured, the mixture

[21] Chatt and Williams, *J.*, 1954, 4404.
[22] Allred and Rochow, *J. Inorg. Nuclear Chem.*, 1958, **5**, 269.
[23] Stock and Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 3323.
[24] Stock and Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 5621.
[25] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.

XUM

being kept either in a 1 cm. cell at 50·0° ± 0·04° (thermostat) in the Unicam S.P. 500 spectrophotometer or, in the one case of the unreactive methiodide of *p*-dimethylaminophenyltricyclohexylsilane, in sealed tubes in a bath at 50·0° ± 0·02°.

While (with the exception of the *p*-dimethylamino-compound, discussed below) rate constants could be duplicated to within ±2%, the random variations in the relative rates of reactions of some pairs of compounds at two or more acid concentrations suggest that the rate constants recorded in Tables 1 and 2 are somewhat less accurate than those obtained in desilylations and degermylations, and we do not feel confident that they are accurate to better than ±3%. We did not attempt to improve on this because the errors involved are unimportant for our purposes.

TABLE 3. *Concentration of* $X{\cdot}C_6H_4{\cdot}SnR_3$, *and wavelength used.*

R	X	10^3 × Concn. (M)	λ (mμ)	R	X	10^3 × Concn. (M)	λ (mμ)
C_6H_{11}	H	1·67	254, 262	C_6H_{11}	*p*-F	1·67	265, 272
	m-Me	1·67	257, 267		*m*-MeO	0·42	276, 284
	p-Me	1·67	257, 267		*p*-MeO	0·83	284
	p-Et	1·67	256, 263		*p*-NMe_2	0·042	262
	p-Pr^i	1·67	255, 262		*p*-$\overset{+}{N}Me_3$	0·167	249
	p-Bu^t	1·67	255, 262		*p*-CO_2H	0·167	253
	p-Ph	0·042	275	Me	H	1·67	259
	o-Ph	0·167	264, 268		*p*-Me	1·67	273
	m-Cl	0·83	262, 269		*m*-Cl	5·0	276
	p-Cl	0·83	259, 269		*p*-Cl	5·0	276
	p-Br	1·67	259, 264	Ph	*p*-MeO	0·83	284

In the sole case of the *p*-dimethylamino-compound, the concentration of acid in the reaction medium is comparable with the concentration of organostannane, and the tricyclohexyltin hydroxide produced in the cleavage removes a significant proportion of the acid. Consequently, first-order rate constants fall throughout each run, and the values of *k* given for this compound in Table 1 are obtained by studying the first 20% of reaction carefully and deriving the rate at zero time by extrapolation. The rate constants could be duplicated within ±5%, and are believed to be accurate to within ±10%.

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THE UNIVERSITY, LEICESTER. [*Received, August 16th*, 1960.]

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108. *Dicyclopentadienyl-tin and -lead.*

By H. P. FRITZ and E. O. FISCHER.

The infrared spectra of dicyclopentadienyl-tin and -lead, in the range 2—40 μ, are recorded and compared with other published values. The results are consistent with previously suggested structures.

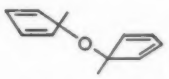
ON the basis of the similarity of the infrared spectra, Fischer and his co-workers [1-3] postulated a sandwich structure, similar to that of ferrocene (I), for dicyclopentadienyl-tin [4] and -lead.[5] They further suggested that the dipole moments of these compounds indicated that the rings were at an angle to one another (II).[3,6] In view of criticism by Dave, Evans, and Wilkinson [7] we have now extended our earlier measurements of the

[1] Fischer and Piesbergen, *Z. Naturforsch.*, 1956, **11***b*, 758.
[2] Fischer, *Z. angew. Chem.*, 1957, **69**, 715.
[3] Fischer and Schreiner, *Chem. Ber.*, 1959, **92**, 938.
[4] Fischer and Grubert, *Z. Naturforsch.*, 1956, **11***b*, 423.
[5] Fischer and Grubert, *Z. anorg. Chem.*, 1956, **286**, 237.
[6] Weiss, *Z. anorg. Chem.*, 1956, **286**, 236.
[7] Dave, Evans, and Wilkinson, *J.*, 1959, 3684.

XUM

infrared spectra. It is well known that the influence of solvents on relatively unstable metal dicyclopentadienyls, which do not have a filled inert-gas configuration for the central atom, must not be overlooked. Thus, the nuclear magnetic resonance spectra of dicyclopentadienyl-mercury [8,7] or -beryllium [9] show only one proton line, although structures

(I) (II)



(III)

involving σ-bonded cyclopentadienyl rings are probable on the basis of the infrared spectra. Dicyclopentadienyliron dicarbonyl shows only two proton signals,[10] one from the π-bonded and one from the σ-bonded ring. In each case a much more complicated nuclear magnetic resonance spectrum would be expected. In infrared spectroscopy, change of solvent sometimes causes remarkable changes in intensity and position of bands. The possibility of formation of addition compounds also must be considered, if the compounds show any donor or acceptor properties.*

For these and other reasons we regard infrared measurements on solutions of this special kind of polar metal dicyclopentadienyl as convenient though sometimes unreliable evidence.

Wilkinson and his co-workers [7] used tetrachloroethylene and carbon disulphide as solvents. The former is suitable when pure, but some important spectral regions cannot be investigated because of absorption by solvent. Carbon disulphide has good solvent properties too, but also, we find, a tendency to form addition compounds with the solute. We therefore conclude that infrared measurements of extremely sensitive and polar compounds are best carried out under the mild conditions of the Nujol or " Hostaflon " (fluorolube) mull technique or on halide discs, if air and moisture can be rigorously excluded. This is ensured in our laboratory, where sensitive substances are handled by means of Schlenk tubes and glove box.

Previously,[11] we listed, amongst others, infrared spectra of the tin and lead compounds in potassium bromide discs [12] and assigned some of the normal frequencies by analogy with ferrocene.[13] We now report the spectra of these two compounds, obtained from freshly resublimed samples as mulls in Nujol and " Hostaflon," respectively, in the range 2—40 μ. The measurements in the far-infrared region are part of an investigation of the position of the metal–ring frequencies of $M(C_5H_5)_2$-compounds.[14] In the Table we include the results reported by Wilkinson and his co-workers,[7] since they claimed that our results were " so much at variance with solution data " given earlier [15] and by them and therefore were " unreliable."

The relative similarity of these spectra with those of ferrocenes was emphasized earlier by Fischer and his co-workers.[1,3]

Clearly spectra of solutions can only be accepted with some reservation. Whilst our mull spectra show a definite difference between the tin and the lead compound, especially in the characteristic region of the CH-deformations,[13,11] the spectra recorded by Wilkinson and his co-workers give very similar values for the two compounds. One cannot explain this difference as that usual between spectra of solid and solution. It is rather the result of an equalizing effect of the solvents on those polar and weakly bonded compounds.

* For recent results in this connexion see Strohmeier and von Hobe (*Z. Elektrochem.*, 1960, **64**, 945).

[8] Strohmeier and Lemmon, *Z. Naturforsch.*, 1959, **14***a*, 109.
[9] Fischer and Hofmann, unpublished work.
[10] Piper and Wilkinson, *J. Inorg. Nuclear Chem.*, 1956, **3**, 104.
[11] Fritz, *Chem. Ber.*, 1959, **92**, 780.
[12] Dr. O. Vohler, Anorg. Inst. T.H., München, kindly supplied these spectra.
[13] Lippincott and Nelson, *Spectrochim. Acta*, 1958, **10**, 307.
[14] Fritz and Schneider, *Chem. Ber.*, 1960, **93**, 1171.
[15] Lindstrom and Barusch, 131st Amer. Chem. Soc. Meeting, 1957, Abstr. 77, as cited in ref. 7.

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Infrared spectra of dicyclopentadienyl-tin and -lead.

$Sn(C_5H_5)_2$				$Pb(C_5H_5)_2$			
KBr disc	Mull	Soln. C_2Cl_4 *	Soln. CS_2 *	KBr disc	Mull	Soln. C_2Cl_4 *	Soln. CS_2 *
		3100sh	3100sh			3090sh	3090sh
3061w	3065m	3094s	3094s		3021w	3082s	3082s
	2967sw						
	2924sw	2919w	2918w	2914w		2917w	2917w
	2882sw			2851sw	2890w		
	2778sw						
	2688sw	2695w	2695w		2632sw	2680w	
	2410sw						
	2356sw				2310sw		
	2262sw	2280w			2288sw	2278w	
	2195sw	2210w				2200w	
	2062sw	2085w			2088sw	2080w	
	1965sw						
	1894sw				1880sw		
	1754w	1750m	1750m				
1739w	1745w				1736w	1732m	1745m
					1721w		1720m
	1689sw				1706sw		
	1656sw						
	1642m						
1631w	1634m				1639w		
					1613w	1622m	
	1585sw						
	1565sw						
	1550w				1546sw		
	1529sw	1532m			1529sw		
	1515sw				1513sw	1515m	
	1504sw				1502sw		
		1482w			1493sw	1482w	
1424m	1428s	1426s				1427s	
				1418w	1416m		
1363m	1366sw		1360m	1382w			1351m
	1342w		1340m		1335sw		
	1258w	1260w	1260w		1263sw	1255w	1260w
		1228w	1228w			1228w	1228w
	1198sw		1193sw		1192sw		1190sw
	1167w		1156w		1164w		1156w
					1149sw		
1112m	1114s		1112s	1111w	1112m		1113s
	1094sw						1082sw
1059w	1060w	1055w	1055w	1057sw	1059w	1055w	1052w
1003s	1004s		1002s	1002m	1007s		1005s
959w	960sw				962sw		
	936sw				929sw		
914w	916sw			913sw	915sw		
890w	890w			898w	890sw		
					881sw		
					861sw		
837w	835w			836w	838w		
	818shw		805w				805w
792s	788shs		780m				780w
	770sh			769sh	766sh		
751s	758s		748ss	756s	752s		750ss
				744s	740s		
664w	663w	666w	666w	663w	662w	666w	666w
544sw	544swbr				588swbr		
	260mbr						

* Dave, Evans, and Wilkinson, ref. 7.

w = weak, m = medium, s = strong, sw = very weak, ss = very strong, sh = shoulder, and br = broad band.

Dave, Evans, and Wilkinson obviously did not consider this, and the question arises whether they measured the spectra of the pure compounds in their normal state at all.

Wilkinson and his co-workers [7] state, quite correctly, that it should be possible to distinguish theoretically between structures (I) [symmetry D_{5d} or D_{5h}] and (II) [symmetry

C_{2v}], and another structure (III), which could be angular [C_1, C_{3v} or other low symmetry].

Structure (III) can be excluded because of the types and low number of intensive bands observed in the infrared spectrum.

For structure (II), for example, with the two rings eclipsed, the selection rules would predict 44 of the 57 possible fundamentals to be active in the infrared region, 7 of which would belong to " skeletal " frequencies of the three-mass model YXY. The 37 ligand frequencies should appear mostly in the range covered by sodium chloride optics. Slight coupling being assumed between vibrations of the two rings, several frequencies will practically coincide, thus being observed as only one band. Nevertheless, more bands should still be observable than for structure (I). Wilkinson and his co-workers [7] state that fewer vibrations will be infrared-active for symmetry group D_{5d} than for D_{5h}, but this is incorrect for sandwich compounds. D_{5d} and D_{5h} symmetry would allow 7 ligand- and 3 " skeletal "-frequencies in the infrared region and 15 Raman-active vibrations for each point group.

Wilkinson and his co-workers deduced that their spectra are consistent with the lower symmetry because of the increased number of bands compared with ferrocene; but their comparison was with a ferrocene spectrum of unknown concentration in carbon tetrachloride [13] and their assignments were incomplete. Hence, their argument is rather speculative.

There are, of course, more efficient methods to prove the absence of structure (I), one being an analysis of the combination bands. The spectra show some weak bands, which (allowing for deviations due to anharmonicity) can be explained as binary combinations of fundamental frequencies, indicating that a D_{5d} or D_{5h} structure is probably absent.

In the far-infrared region we found only one band, which can be assigned with some certainty to a fundamental frequency, for the tin compound and none for the lead compound.

If the structure of the molecules, which we assume to be analogous, were linear (I), only the doubly degenerate, asymmetric ring-tilt and the asymmetric metal–ring stretching vibration would be observable in the range to 40 μ, the doubly degenerate ring–metal–ring deformation lying at much lower frequencies.[13]

If the structure is angular (II) there would be two asymmetric ring-tilt and one metal–ring stretching vibrations within the same range, and the results obtained with ferrocene and ruthenocene [13] suggest that the remaining fundamentals of the YXY model active in the infrared region would probably lie at lower frequencies.

Since the asymmetric ring-tilt vibration does not occur lower than 400 cm.$^{-1}$ in all other metal dicyclopentadienyls [14] the corresponding frequencies of the tin and the lead compound will be tentatively assigned to the very weak bands at 544 and 588 cm.$^{-1}$, respectively, although deformation frequencies are likely to occur in the same range. Their broad contour might be due to splitting, caused by removal of the degeneracy.

Only the 260 cm.$^{-1}$ band of the tin compound can be assigned reasonably securely to asymmetric metal–ring stretching. In tin tetrabromide the Sn–Br stretching frequency occurs at 279 cm.$^{-1}$, so our assignment to metal–ring stretching can be regarded as plausible.

It is now possible to refine Fischer's earlier concept. Accepting the structure to be angular (II), we can assume a non-linear configuration YXY for the molecules if one cyclopentadienyl ligand is regarded as one point of mass Y in an approximation used for dicyclopentadienyl-iron and -ruthenium.[13] The force constant of the metal–ring bond being taken as approximately the same as in other metal dicyclopentadienyls of comparable sensitivity,[14] that is *ca.* $1{\cdot}5 \times 10^5$ dynes/cm., an angle of *ca.* 108° between the two axes perpendicular to the planes of the rings is obtained.[16] The assumption of a sp^2-hybridisation for the tin atom, which Wilkinson *et al.* discuss too, seems to be in good accord with

[16] Calculated by using an approximate formula given by Herzberg, " Molecular Spectra and Molecular Structure, Vol. II, Infrared and Raman Spectra of Polyatomic Molecules," van Nostrand Corp., Inc., Princeton, 1956, p. 169.

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this value, if the deviation from 120° is considered as due to an increase of *p*-character for the bonding orbitals and an increase of *s*-character for the third sp^2 hybrid orbital, which should contain the remaining two electrons as a lone pair. Dave, Evans, and Wilkinson agree with our concept of predominantly σ-bonding with some additional π-bonding between metal atoms and rings in dicyclopentadienyltin and probably also in the lead compound.

Experimental

Pure samples of dicyclopentadienyl-tin [4] and -lead [5] were resublimed and immediately used for infrared spectral measurements. The Nujol had been heated for some hours in a high vacuum and was cooled in an atmosphere of purified nitrogen. The " Hostaflon " (fluorolube) was treated similarly. The infrared measurements were made on a Perkin-Elmer spectrophotometer model 21 with sodium chloride and cæsium bromide optics. In order to reduce stray light and water absorption in the far-infrared region, a " reststrahlen " filter was used, and the spectrometer and its sample compartment were flushed with dry nitrogen. The mulls were placed between sealed sodium chloride or cæsium bromide windows. The spectra of potassium bromide discs were obtained on a different spectrometer of the same model with sodium chloride optics.[12]

The authors thank the " Münchner Universitätsgesellschaft " for the purchase of the cæsium bromide prism and the " reststrahlen " filter unit, and the Farbwerke Hoechst A.G. for a gift of Hostaflon oil.

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109. *A New Triterpene from the Hong Kong Ericaceae: an Epoxyglutinane from* Rhododendron westlandii.

By H. R. Arthur and (Miss) W. H. Hui.

A new triterpene, $C_{30}H_{50}O$, has been isolated from the leaves of *Rhododendron westlandii*. This compound, which has been related to glutinane, has been shown not to contain hydroxyl or carbonyl groups. Evidence for a cyclic oxide group has been obtained and structures (III and IV) are considered possibilities.

It has been shown [1] that ursolic acid, cerin, friedelin, epifriedelanol,* and a new triterpene * (from *Rhododendron westlandii*) occur in Hong Kong species of the Ericaceae. The new compound, $C_{30}H_{50}O$ (one atom of oxygen was shown to be present by difference and by a direct oxygen determination), which was twice chromatographed and then recrystallised before use, did not form acyl or carbonyl derivatives under mild or forcing conditions, and absence of hydroxyl and carbonyl groups was confirmed by comparison of its infrared spectrum with those for glutin-5(10)-en-3β-ol (I) and glutin-5(10)-en-3-one (Ia). It is thus presumably an epoxide, and in agreement with this it was eluted from the chromatographic column before the alcoholic and ketonic triterpenoids which the extract also contained.

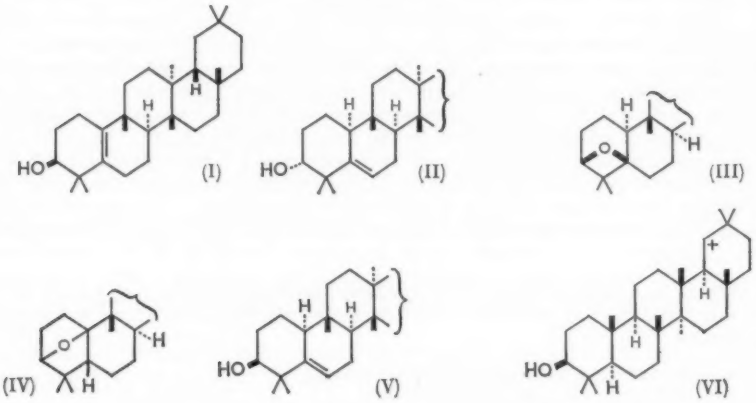
The new compound, which is stable to boiling alkali, is isomerised almost quantitatively under mild acid conditions to glutin-5(10)-en-3β-ol (I). Attempted oxidation with chromic and sulphuric acid gave a mixture of ketones.[2] These ketones could not be separated but were identified as glutin-5(10)-en-3-one and glutin-5-en-3-one since the mixture was reduced to the corresponding mixed alcohols, (I) and glutin-5-en-3α-ol (II), whose acetates were separated by recrystallisation. The ketones were presumably obtained by oxidation

* By error the sign of rotation was reversed for these compounds in a previous paper.[1b]

[1] (*a*) Arthur and Hui, *J.*, 1954, 2782, 4683; (*b*) Arthur, Lee, and Ma, *J.*, 1956, 1461.
[2] Beaton, Spring, Stevenson, and Stewart, *Tetrahedron*, 1958, **2**, 246.

of the alcohols (I) and (II) derived from the oxide by acid-isomerisation. In a separate experiment aqueous acid was found to isomerise the oxide to the alcohol mixture.

The oxide, unlike the alcohols (I) and (II) into which it can be isomerised, did not absorb at low wavelengths in the ultraviolet region (absence of tri- and tetra-substituted double bonds). Its light absorption throughout the entire ultraviolet region, in fact, was



negligible; it gave no colour with tetranitromethane whereas both alcohols gave strong colours; it did not undergo catalytic reduction or react with osmium tetroxide. These facts, considered together with the absence of hydroxyl and carbonyl groups and the ready isomerisation to the alcohol (I), suggest that the compound is a 3,*x*-epoxyglutinane, and structure (III) or (IV) seems probable.*

The oxide was recovered unchanged after treatment with lithium aluminium hydride in various solvents, so the possibility that it is a 1,2-epoxide seems to be excluded. Reaction with boron trifluoride in ether was unsuccessful in that the mixture of alcohols (I) and (V), but no ketone, was obtained. The oxide shows absorption in the region 980—970 cm.$^{-1}$ which might possibly represent that of a cyclic oxide group.[3] In a modification of the test [4] for cyclic oxides, using periodic acid, the oxide appeared to give a positive reaction, but we considered that the test was unreliable for triterpenoid compounds.

Glutin-5-en-3-one (glutinone, alnusenone) was first reported from *Alnus glutinosa* by Chapon and David.[5] Corey and Ursprung [6] converted friedelin into glutinone and the path which they used was re-investigated by Beaton *et al.*[2] who obtained mixed ketones as products [glutin-5-en-3-one and glutin-5(10)-en-3-one]; and the close relation between glutinone and friedelin has been noted.[2]

It is considered [7] that the biogenesis of the pentacyclic triterpenoids takes place from a squalenoid precursor *via* a common ion (VI or equivalent), and Beaton *et al.*[2] consider that degeneration of this ion may give rise to β-amyrin, taraxerol (taraxerone), glutin-5-en-3β-ol (glutinone), friedelin, and other compounds. In view of this, it is worth noting that, among other products, taraxerol and taraxerone occur in Canadian peat moss,[8] as do these two compounds [9] with glutinone [5] in *A. glutinosa*. 5β-Friedelan-3β-ol, with other triterpenoid

* We acknowledge gratefully suggestions from a Referee about the structure of the oxide.

[3] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1956.
[4] Fuchs, Waters, and Vanderwerf, *Analyt. Chem.*, 1952, **24**, 1514.
[5] Chapon and David, *Bull. Soc. chim. France*, 1953, 333.
[6] Corey and Ursprung, *J. Amer. Chem. Soc.*, 1955, **77**, 3667.
[7] Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.
[8] Ives and O'Neill, *Canad. J. Chem.*, 1958, **36**, 927.
[9] Koller, Hiestand, Dietrich, and Jeger, *Helv. Chim. Acta*, 1950, **33**, 1050.

compounds, occurs in humidified peat,[10] and this compound with friedelin, β-amyrin,[11] and the new epoxyglutinane occurs in *R. westlandii*.

Experimental

Analyses were by Dr. Zimmermann, Melbourne. M. p.s were taken on a Kofler block. Alumina used was of B.D.H. analysis grade; light petroleum had b. p. 60—80°. Rotations are for $CHCl_3$ solutions. Infrared spectra were taken for Nujol mulls on a Model 137 Infracord spectrophotometer. The spectrum of the oxide was also checked on a large instrument. Ultraviolet spectra were taken for EtOH solutions on a S.P. 500 Unicam instrument.

Isolation and Properties of the New Oxide.—Dried leaves (6·0 kg.) of *Rhododendron westlandii* were extracted with light petroleum, and the total extract, after removal of epifriedelanol as described in a previous paper,[1b] was chromatographed on alumina (2 kg.). Elution with light petroleum gave a wax from the first 500 ml. of eluate, and from the next 1500 ml. an *oxide*, which after two recrystallisations from light petroleum separated as stout needles (5·0 g.), m. p. 201—202°, $[\alpha]_D$ +74·8° (*c* 1·08) (Found: C, 84·4; H, 11·5; O, 4·0. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8; O, 3·8%). Repeated chromatography and recrystallisation did not alter these properties. The oxide is soluble in chloroform, benzene, and light petroleum but very sparingly soluble in ethanol. It gave no colour with tetranitromethane but a deep red colour in the Liebermann–Burchardt test. It was identical with a triterpenoid substance reported previously [1b] from this plant. The oxide was recovered unchanged almost quantitatively after attempted benzoylation and acetylation under mild and forcing conditions, and after being heated with semicarbazide hydrochloride in aqueous pyridine for 12 hr. It did not react with potassium hydroxide in aqueous dioxan or with lithium aluminium hydride in boiling diethyl ether, tetrahydrofuran, or dibutyl ether, and it was recovered unchanged after being treated with osmium tetroxide in chloroform–pyridine for 15 days. It did not react with potassium cyanide in boiling ethylene glycol or with methylmagnesium iodide in boiling ether for 14 hr.

Isomerisation of the Oxide.—(a) *With hydrogen chloride.* Hydrogen chloride was passed into a solution of the oxide (0·5 g.) in dry chloroform (75 ml.). The solvent was removed in a vacuum and the residue crystallised from acetone, as plates of glutin-5(10)-en-3β-ol (0·45 g.), m. p. 243—244·5°, $[\alpha]_D$ −35·7° (*c* 1·01), λ 2070 Å (ε 5880) (Found: C, 84·9; H, 12·0. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). This product was also obtained, quantitatively, on treatment of the oxide with concentrated hydrobromic acid in acetic acid. It gave an acetate (acetic anhydride and pyridine) that separated from benzene as plates, m. p. 300—302°, $[\alpha]_D$ −18·0° (*c* 1·05) (Found: C, 81·7; H, 10·8. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%); glutin-5(10)-en-3-one, prepared by oxidation [12] with chromium trioxide of the alcohol (0·18 g.) in stabilised acetone, separated from acetone as prisms (0·14 g.), m. p. 255—257°, $[\alpha]_D$ −92·5° (*c* 0·80), $\lambda_{max.}$ 2900 (ε 87), 2070 Å (ε 5680) (Found: C, 84·8; H, 11·4. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%). The alcohol, its acetate, and the ketone had infrared spectra identical with those of authentic specimens.

(b) *Attempted oxidation under aqueous acid conditions.* The oxide (1·0 g.) in stabilised acetone (1 l.) was oxidised as above.[12] Concentration of the solution yielded prisms (0·8 g.) of a mixture, m. p. 247—248·5° (Found: C, 85·1; H, 11·7. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%) [Beaton *et al.*[2] give m. p. 247—249° for the mixed crystal of glutinone and glutin-5(10)-en-3-one], which was almost quantitatively converted into an oxime, m. p. 280—285° (Found: C, 81·5; H, 11·1; N, 3·4. Calc. for $C_{30}H_{49}NO$: C, 81·9; H, 11·2; N, 3·2%). The ketone mixture (0·47 g.) in dioxan (70 ml.) was boiled under reflux with sodium borohydride for 3 hr. The product (0·46 g.), which could not be purified by recrystallisation or chromatography,[2] was treated with acetic anhydride and pyridine at room temperature for 4 days. The product (0·41 g.) afforded (i) glutin-5(10)-en-3β-yl acetate which separated slowly as plates (0·26 g.) and after two recrystallisations from benzene had m. p. and mixed m. p. 299—301°, $[\alpha]_D$ −20·7° (*c* 1·55), and (ii) fine needles (0·15 g.) of glutin-5-en-3α-yl acetate,[13] m. p. 226—229°, $[\alpha]_D$ +42·9° (*c* 0·23), λ 2070 Å (ε 4460) (Found: C, 81·7; H, 10·9. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%),

[10] McLean, Rettie, Spring, *Chem. and Ind.*, 1958, 1515.
[11] Unpublished work in this laboratory.
[12] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.
[13] Beaton, Spring, and Stevenson, *J.*, 1955, 2616.

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which was obtained from the acetic anhydride–pyridine filtrate by addition of water followed by crystallisation from benzene–methanol. The acetates had infrared spectra identical with those of authentic samples.

(c) *With boron trifluoride in ether.* A solution of the oxide (0·9 g.) in ether (160 ml.) and 47% boron trifluoride–ether complex (4 ml.) was left at room temperature. Crystals quickly appeared. After 3 hr. water was added to decompose the complex. The washed ethereal phase was dried (Na_2SO_4) and distilled. The residual mixture (0·9 g.) could not be purified by recrystallisation or by chromatography. On treatment with acetic anhydride and pyridine for 2 days at room temperature, crystals which were deposited were collected and recrystallised from benzene. Glutin-5(10)-en-3β-yl acetate (0·76 g.), m. p. 298—299° (identified by mixed m. p. and infrared spectrum), separated. To the pyridine–acetic anhydride filtrate, water was added and the precipitate was collected and recrystallised from benzene–methanol. Flattened needles (0·14 g.) of glutin-5-en-3β-yl acetate, m. p. 191—193°, $[\alpha]_D$ +70·7° (*c* 1·85), separated {Paton *et al.*[14] give m. p. 192—194°, $[\alpha]_D$ +79°} (Found: C, 81·9; H, 11·4. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). A similar alcohol mixture, obtained after attempted hydrogenation in chloroform with Adams catalyst and also separated by acetylation, was shown to contain glutin-5(10)-en-3β-ol and probably glutin-5-en-3β-ol.

The authors thank Professor J. E. Driver for interest, Dr. J. McLean (Royal College of Science and Technology, Glasgow) for arranging comparisons of infrared spectra of some of our compounds with those of authentic samples, Mr. H. C. Tang (Government Herbarium, Hong Kong) for identification of plant material, and the Research Grants Committee of the University of Hong Kong for grants-in-aid.

University of Hong Kong, Hong Kong. [*Received, April 11th,* 1960.]

[14] Paton, Spring, and Stevenson, *J.*, 1958, 2640.

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110. *Homolytic Aromatic Substitution. Part XXI.* The Arylation of Benzotrihalides.*

By D. H. Hey, F. C. Saunders, and Gareth H. Williams.

Experiments have been carried out on the phenylation and *p*-nitrophenylation of benzotrichloride with benzoyl peroxide and *p*-nitrobenzoyl peroxide respectively. The reaction of benzotrifluoride with benzoyl peroxide has also been investigated. The ratios of the isomeric arylbenzotrihalides obtained in these reactions have been determined with the aid of infrared spectroscopy and gas–liquid chromatography. The results show significant differences from those reported by other workers. In particular, the absence of *ortho*-substitution in the phenylation, and of *para*-substitution in the *p*-nitrophenylation, of benzotrichloride, reported by Dannley and Sternfeld, are not substantiated.

Experiments on the homolytic arylation of benzotrihalides have been reported by two groups of workers. Dannley and Sternfeld[1] investigated the thermal decomposition of benzoyl peroxide in benzotrifluoride, which was found to give negligible reaction at the trifluoromethyl group but gave a mixture of the three isomeric trifluoromethylbiphenyls in 50% yield. The composition of the mixture was reported as *ortho* 18%, *meta* 40%, and *para* 42%. In similar reactions of benzoyl peroxide, *p*-chlorobenzoyl peroxide, and *p*-nitrobenzoyl peroxide with benzotrichloride, these workers reported the total absence of substitution at the *ortho*-position, a decrease in reaction at the side-chain (57, 16, and 0% respectively), and an increase in substitution at the *meta*-position (60, 83, and 100% respectively). The phenylation of benzotrifluoride by means of both benzoyl peroxide and

* Part XX, *J.*, 1960, 3787.

[1] Dannley and Sternfeld, *J. Amer. Chem. Soc.*, 1954, **76**, 4543.

N-nitrosoacetanilide has also been reported by Rondestvedt and Blanchard [2] and the products from both reactions were reported to have the composition *ortho* 20%, *meta* 40%, and *para* 40%, in good agreement with the results obtained by the earlier workers. In addition, the total rate factor for the phenylation of benzotrifluoride with respect to benzene was shown to be 0·99 by means of competitive experiments with pyridine. More recently Dannley, Weigand, and Pavlos [3] have reported the reactions of *p*-methoxy- and *m*-nitrobenzoyl peroxide with benzotrichloride which gave, respectively, 51% and 62% substitution at the *meta*-position and 49% and 38% substitution at the *para*-position. Again, in neither case was any substitution at the *ortho*-position observed. The above results appeared to show a number of unusual features and for this reason it was considered desirable to re-investigate some of these reactions.

The steric inhibition to free-radical attack at the *ortho*-position with reference to a large substituent has been well recognised,[4,5] but the complete inhibition of reaction at the *ortho*-position with respect to the trichloromethyl group with phenyl, *p*-chlorophenyl, and *p*-nitrophenyl radicals is very surprising. Further, the reported occurrence of 100% substitution at the *meta*-position in the *p*-nitrophenylation of benzotrichloride is a unique observation. The results now reported on the phenylation and *p*-nitrophenylation of benzotrichloride and on the phenylation of benzotrifluoride reveal some marked differences from those reported by the earlier workers.

The reactions of benzoyl peroxide and *p*-nitrobenzoyl peroxide with benzotrichloride were carried out at 80° with a molar ratio of 0·025 : 1 and 0·018 : 1 respectively. Those carried out by Dannley and Sternfeld [1] were conducted at 75° and at 100° with molar ratios of 0·125 and 0·0625 respectively. The reaction with benzotrifluoride was carried out at 80° with a molar ratio of 0·018 : 1. The same experiment was carried out by Dannley and Sternfeld [1] at 75° and at 100° with a molar ratio of 0·0625 : 1 and by Rondestvedt and Blanchard [2] at 80—100° with a molar ratio of 0·030 : 1. The products were worked up by methods similar to those used by the previous investigators. The biaryl products from the reactions with benzotrichloride were hydrolysed to the corresponding arylbenzoic acids, which were then esterified with diazomethane. The mixtures of methyl biphenylcarboxylates were analysed by gas–liquid chromatography and those of the methyl *p*-nitrobiphenylcarboxylates by infrared spectroscopy. The mixtures of trifluoromethylbiphenyls were isolated by distillation and analysed by gas–liquid chromatography. The previous workers used infrared spectroscopy for all their analyses.

Experimental

Preparation of Reagents.—Benzoyl peroxide and nitrobenzene were purified as described in Part II.[6] *p*-Nitrobenzoyl peroxide was prepared by Hey and Walker's method.[7] 1,1,2,2-Tetrachloro-1,2-diphenylethane, m. p. 160—161°, was prepared by Fuson and Ross's method.[8] Benzotrichloride and benzotrifluoride were dried ($CaCl_2$), filtered, and distilled in a 4 ft. helix-packed column fitted with a heating jacket. The former was collected at 96°/18 mm. and the latter at 102·5°/760 mm. 2-, 3-, and 4-Trifluoromethylbiphenyl were supplied by Professor J. C. Tatlow of the University of Birmingham, and had m. p. 15° (b. p. 102—103°/8 mm.), m. p. 26·5°, and m. p. 70° respectively.

Isomeric Methyl Biphenylcarboxylates.—Methyl biphenyl-2-carboxylate was prepared by Grieve and Hey's method,[9] the crude ester being hydrolysed to biphenyl-2-carboxylic acid, m. p. 114°, which was re-esterified with diazomethane. The pure ester had b. p. 96—98°/0·1 mm., n_D^{18} 1·5855 (Found: C, 79·1; H, 5·7. Calc. for $C_{14}H_{12}O_2$: C, 79·3; H, 5·7%). In a similar

[2] Rondestvedt and Blanchard, *J. Org. Chem.*, 1956, **21**, 229.
[3] Dannley, Weigand, and Pavlos, 136th Meeting Amer. Chem. Soc., Sept., 1959, 18P.
[4] Cadogan, Hey, and Williams, *J.*, 1953, 3412; 1954, 3352.
[5] Hey, Pengilly, and Williams, *J.*, 1956, 1463.
[6] Augood, Hey, and Williams, *J.*, 1952, 2094.
[7] Hey and Walker, *J.*, 1948, 2216.
[8] Fuson and Ross, *J. Amer. Chem. Soc.*, 1933, **55**, 722.
[9] Grieve and Hey, *J.*, 1938, 111.

reaction methyl *m*-aminobenzoate hydrochloride (65 g.) was diazotised and in reaction with benzene gave crude methyl biphenyl-3-carboxylate (7·8 g.) as a yellow oil, b. p. 180—185°/15 mm. After purification on an alumina column with benzene–light petroleum as eluent, the oil (7·5 g.) was hydrolysed with aqueous sodium hydroxide to biphenyl-3-carboxylic acid, m. p. 161° (from benzene). Esterification with diazomethane gave the *methyl ester* (3·41 g.), b. p. 88—89°/0·05 mm., which solidified. Recrystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 48—49° (Found: C, 79·1; H, 5·8. $C_{14}H_{12}O_2$ requires C, 79·3; H, 5·7%). Methyl biphenyl-4-carboxylate was prepared by two methods: (*a*) 4-Methylbiphenyl, prepared by Gomberg and Pernert's method,[10] was oxidised with potassium permanganate to biphenyl-4-carboxylic acid, m. p. 222° (from ethanol), esterification of which by the Fischer–Speier method gave the methyl ester, m. p. 116·5° (from aqueous methanol). (*b*) Diazotised methyl *p*-aminobenzoate (50 g.) and benzene, as described above for the corresponding reaction with the *ortho*- and *meta*-isomers, gave a crude methyl ester, b. p. 155—165°/20 mm., which solidified. Four recrystallisations from methanol gave the pure ester (10·64 g.), m. p. 116·5° alone and on admixture with the compound prepared by method (*a*) (Found: C, 79·0; H, 5·7%).

Methyl 4′-Nitrobiphenyl-2-carboxylate.—2-Methyl-4′-nitrobiphenyl (8 g.), kindly supplied by Dr. J. K. Hambling, in 2% aqueous potassium permanganate (600 ml.) was heated with stirring on a steam-bath for 24 hr. Sulphur dioxide was passed into the cooled solution and the precipitated acid was collected, dried, and crystallised from ethanol (7 g.; m. p. 226—227°). Esterification with diazomethane gave methyl 4′-nitrobiphenyl-2-carboxylate, m. p. 78° (from ethanol) (Found: C, 65·3; H, 4·4; N, 5·1. Calc. for $C_{14}H_{11}NO_4$: C, 65·4; H, 4·3; N, 5·4%). Dannley and Sternfeld [1] reported m. p. 75—76°.

Methyl 4′-Nitrobiphenyl-3-carboxylate.—4′-Nitrobiphenyl-3-carboxylic acid was prepared by two methods: (*a*) Biphenyl-3-carboxylic acid (2·5 g.), prepared as described above, in a mixture of fuming nitric acid (3·5 ml.) and glacial acetic acid (10 ml.), was boiled under reflux for 2 hr. The mixture was cooled to 0° and the solid product was collected, washed with water, and crystallised from ethanol to give 4′-nitrobiphenyl-3-carboxylic acid (0·5 g.), m. p. 232° (Found: N, 5·2. Calc. for $C_{13}H_9NO_4$: N, 5·8%). (*b*) *m*-Toluidine (107 g.) in concentrated hydrochloric acid (185 ml.) and water (50 ml.) was cooled in ice–salt and diazotised with sodium nitrite (70 g.) in water (90 ml.). The resulting solution after filtration was added slowly to stirred nitrobenzene (1000 ml.) and 40% aqueous sodium hydroxide (275 ml.) at 5°. After 3 hr. the temperature was allowed to rise to room temperature and stirring was continued for 48 hr. The nitrobenzene layer was separated, washed with dilute hydrochloric acid and then with water, and dried ($CaCl_2$). Excess of nitrobenzene was removed by distillation and the tarry residue was extracted with light petroleum (b. p. 60—80°; 6 × 100 ml.). Removal of the solvent by distillation left a red oil, which was distilled under reduced pressure. The fraction, b. p. 190—210°/15 mm., was chromatographed on an alumina column and eluted with benzene. Removal of the solvent from the eluate gave a red oil, which was further purified by shaking it in benzene solution with concentrated sulphuric acid (8 × 5 ml.). The resulting yellow solution was washed with water and dried (Na_2SO_4). Removal of the benzene left a yellow oil, which was distilled at 0·05 mm. The main distillate was collected at 98—100° as a pale yellow oil (6·4 g.). A second fraction was collected at 116—118° and solidified (1·85 g.); on recrystallisation from light petroleum (b. p. 60—80°) this gave *3-methyl-4′-nitrobiphenyl* in pale yellow needles, m. p. 55° (Found: C, 73·0; H, 5·4; N, 6·2. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2; N, 6·6%). A further quantity of 3-methyl-4′-nitrobiphenyl (0·4 g.) separated gradually from the main distillate, which consisted of a mixture of the isomeric 3-methylnitrobiphenyls. 3-Methyl-4′-nitrobiphenyl (0·5 g.) in glacial acetic acid (10 ml.) was heated on a steam-bath with stirring and oxidised by the slow addition of chromium trioxide (0·5 g.) in the same solvent (150 ml.). Stirring of the hot solution was continued overnight, after which it was added to water (500 ml.) and cooled to 5°. The precipitated solid was collected, washed with water, and shaken with saturated aqueous sodium hydrogen carbonate (100 ml.). After filtration from unchanged 3-methyl-4′-nitrobiphenyl, acidification of the solution gave 4′-nitrobiphenyl-3-carboxylic acid (0·1 g.), m. p. 230—231° alone and on admixture with the acid prepared by method (*a*) above. A similar oxidation was carried out with aqueous potassium permanganate.

Esterification of the acid with ethereal diazomethane in the normal manner gave the methyl ester, m. p. 116—117° (from ethanol), in 95% yield. Dannley and Sternfeld [1] reported m. p. 112·5—113°.

[10] Gomberg and Pernert, *J. Amer. Chem. Soc.*, 1926, **48**, 1372.

XUM

Methyl 4′-Nitrobiphenyl-4-carboxylate.—4′-Nitrobiphenyl-4-carboxylic acid, m. p. 338—340°, was prepared (*a*) by the successive nitration and oxidation of 4-methylbiphenyl,[11] and (*b*) by the preparation of 4-methyl-4′-nitrobiphenyl from *p*-toluidine and nitrobenzene followed by oxidation.[11] Esterification of the acid with ethereal diazomethane gave the methyl ester, m. p. 188—189° (from ethanol) (Found: C, 64·8; H, 4·7. Calc. for $C_{14}H_{11}NO_4$: C, 65·4; H, 4·3%). The same ester was prepared as follows: *p*-Nitroaniline (138 g.) in concentrated hydrochloric acid (270 ml.) and water (50 ml.) was diazotised in the normal manner with sodium nitrite (70 g.) in water (150 ml.), and added slowly to cold stirred methyl benzoate (900 ml.). To this vigorously stirred mixture, maintained at 0—5°, was added dropwise a solution of hydrated sodium acetate (320 g.) in water (800 ml.). After 2 hr. the temperature was allowed to rise to room temperature and stirring was continued for 36 hr. The organic layer was separated, washed with hydrochloric acid and with water, and dried (Na_2SO_4). The excess of methyl benzoate was removed by distillation and the residue was distilled at 0·05 mm., to give the following fractions: (*a*) b. p. 40—60° (5 ml.); (*b*) b. p. 155—170° (1·5 g.); and (*c*) b. p. 170—185° (*ca.* 50 g.). Fraction (*a*) consisted of methyl benzoate; fractions (*b*) and (*c*) were red oils, which solidified. Fraction (*c*) was digested with cold acetone and the extract was evaporated to dryness. Crystallisation of the residue from ethanol gave pale yellow methyl 4′-nitrobiphenyl-2-carboxylate (44 g.), m. p. 77—78° alone and on admixture with the compound prepared as above. The infrared spectra were identical. The same product was obtained from fraction (*b*). The residue, which remained after the digestion of fraction (*c*) with cold acetone, was boiled with ethanol and charcoal. After filtration and partial evaporation this solution deposited methyl 4′-nitrobiphenyl-4-carboxylate (5·8 g.), m. p. 188° (from ethanol) alone and on admixture with the compound prepared as above. The infrared spectra of the two samples were identical. The m. p. recorded by Dannley and Sternfeld [1] for the 4-carboxylate is 135—135·5°, and it was for this reason that two independent methods of preparation were undertaken.

Analytical Procedures.—The infrared spectrographic measurements were made on a Grubb–Parsons double-beam spectrometer, equipped with a rock-salt optical system and an automatic pen-recorder. Gas–liquid chromatographic analyses were carried out on a 4′ glass column of 4 mm. diameter. Nitrogen was used as eluent and a Martin gas density balance was used as detector. Analysis of the esters was carried out at 245°, over Celite 545 coated with Apiezon grease (type L, 20% w/w). Analysis of the trifluoromethylbiphenyls was carried out at 135° over an Epikote resin (A.C.D.S. 834) as stationary phase. Retention times were measured relative to n-hexadecane.

The Reaction between Benzoyl Peroxide and Benzotrichloride. Preliminary Experiments.—It was shown that benzotrichloride is converted quantitatively into benzoic acid by boiling it under reflux with an excess of 10% aqueous sodium hydroxide for 12 hr. and that the benzoic acid isolated can be converted quantitatively into its methyl ester with diazomethane. The mixtures of isomeric trichloromethylbiphenyls formed in the phenylation of benzotrichloride were boiled under reflux with alkali twice, in order to ensure complete hydrolysis. The quantitative esterification of the acids was established by the conversion of a mixture of benzoic acid and the three biphenylcarboxylic acids into a mixture of the four esters with diazomethane. The methyl benzoate could be distilled at 76—80°/12 mm., whereas the biphenyl esters distilled at 70—80°/0·05 mm. The weights of the two fractions confirmed that the esterifications and separation were quantitative. Examination of the vapour-phase chromatograms showed the absence of methyl methoxybenzoates in the products obtained from the phenylation of benzotrichloride at 80° with benzoyl peroxide, when they were worked up by hydrolysis and esterification. Methyl methoxybenzoates could be formed by hydrolysis and subsequent methylation of the products of benzoyloxylation of benzotrichloride. 1,1,2,2-Tetrachloro-1,2-diphenylethane was shown to be stable to boiling 10% aqueous sodium hydroxide for 14 hr.

Reactions with Benzoyl Peroxide.—Experiments 1—6 (see Table 1) were carried out with benzoyl peroxide (6 g.) in benzotrichloride (200 g.) at 80° for 72 hr. The flask was fitted with an air-condenser and calcium chloride guard-tube. The mixture was then extracted with cold saturated aqueous sodium hydrogen carbonate (5 × 50 ml.) to remove free benzoic acid, and the organic layer was washed with water and dried ($CaCl_2$). The aqueous layer was shaken with benzene and these washings were added to the organic layer. The benzoic acid was recovered from the combined alkaline washings by acidification and extraction with ether. The main organic layer was distilled slowly using a 25 cm. helix-packed column surrounded by

[11] Grieve and Hey, *J.*, 1932, 1891, 1893.

XUM

a heating jacket. Benzene was collected at atmospheric pressure and the excess of benzotrichloride at 20 mm. The residue was boiled under reflux twice with 10% aqueous sodium hydroxide for 14 hr. When cold, the mixture was extracted with benzene and the organic layer separated. The alkaline layer was acidified with hydrochloric acid, and the precipitated solid was digested with aqueous sodium hydrogen carbonate until it was alkaline. This mixture was heated to coagulate inorganic matter, cooled, and filtered. The filtrate was acidified and extracted with ether, and the acidic residue obtained on removal of the solvent

TABLE 1.

Experiment no.:	1	2	3	4	5	6
Free benzoic acid (g.)	0·49	0·51	—	0·48	—	—
Chlorobenzene (g.).....	—	—	2·42	—	2·40	2·45
Tetrachlorodiphenylethane (g.)	2·04	2·28	2·28	2·52	2·25	2·32
Biaryls (g.)	0·756	0·854	0·821	0·721	0·850	0·885
Residue (g.)	0·118	0·121	0·219	0·290	0·219	0·179

at room temperature was esterified with an excess of ethereal diazomethane. After removal of ether and excess of diazomethane the residual esters (*ca.* 5 ml.) were transferred to a micro-distillation flask and distillation gave two fractions: (*a*) b. p. 76—80°/12 mm. and (*b*) b. p. 70—80°/0·05 mm. (see Table 1). A small residue was left which did not distil at 150°/0·05 mm.

The organic layer from the hydrolysis was dried ($CaCl_2$) and the solvents were removed by distillation. The residue was adsorbed on alumina and eluted, first with light petroleum (b. p. 60—80°) which gave an orange solid, secondly with benzene which gave a dark red tar, and thirdly with chloroform which gave a dark tar. Recrystallisation of the orange solid, first, from ethanol and finally from glacial acetic acid gave tetrachlorodiphenylethane, m. p. 155°, which was not depressed on admixture with an authentic specimen (m. p. 160—161°) (Found: C, 52·4; H, 3·2; Cl, 44·3. Calc. for $C_{14}H_{10}Cl_4$: C, 52·5; H, 3·2; Cl, 44·3%). The infrared spectra of the two samples were identical.

In experiments 3, 5, and 6, in which the chlorobenzene formed was estimated, the benzotrichloride was removed by distillation under reduced pressure *without* previous removal of the benzoic acid by extraction with sodium hydrogen carbonate solution. The first 25—30 ml. of benzotrichloride were collected separately and it was assumed that any chlorobenzene formed would be found in this fraction. The fraction was diluted with light petroleum (10 ml.; b. p. 100—120°), and the light petroleum was slowly distilled off. This process was repeated six times and the total distillate was treated with concentrated sulphuric acid and fuming nitric acid to convert any chlorobenzene into 1-chloro-2,4-dinitrobenzene, which was collected and weighed. The method was tested with mixtures of known composition and a small correction factor was applied in order to allow for the non-quantitative nature of the method. The results obtained in Experiments 1—6 are given in Table 1. These results correspond to 66% of side-chain attack and 34% of nuclear attack. The procedure described above does not permit the measurement of the amount of benzoic acid formed by the hydrolysis of esters, since benzotrichloride itself is readily hydrolysed and any benzoic acid formed by the hydrolysis of residual solvent is obtained together with any formed from esters.

Determination of the Isomer Ratios in the Methyl Biphenylcarboxylates derived from the Products of the Phenylation of Benzotrichloride.—(a) *Infrared method.* Examination of the spectra of methyl biphenyl-2-carboxylate as a liquid film and of the 3- and 4-isomers as Nujol mulls led to the selection of the following wavelengths for analytical purposes: *ortho*, 794·9 cm.$^{-1}$, *meta*, 845·2 cm.$^{-1}$, *para*, 863·5 cm.$^{-1}$. Nitromethane was used as solvent but analysis of mixtures of known composition revealed that this method afforded only a determination of the *para*-isomer with any degree of accuracy (±4%). (b) *Gas–liquid chromatographic method.* Retention volumes were determined in turn for n-hexadecane and the three methyl biphenylcarboxylates. Determinations were then made with the products derived from the phenylation of benzotrichloride. The accuracy of the method was determined by its application to the analysis of a typical mixture of known composition. The results obtained are given in Table 2.

The Reaction between p*-Nitrobenzoyl Peroxide and Benzotrichloride.*—In experiments 7—10 *p*-nitrobenzoyl peroxide (6 g.) was allowed to decompose in benzotrichloride (200 g.) at 80° for 72 hr. as in the preceding experiments. The mixture was extracted with aqueous sodium hydrogen carbonate (6 × 50 ml.) and acidification of the extract gave *p*-nitrobenzoic acid,

XUM

m. p. 235—236°. Excess of benzotrichloride was removed under reduced pressure from the dried ($CaCl_2$) organic layer, and the residue was boiled under reflux twice with 10% aqueous sodium hydroxide (100 ml.) for 12 hr. The alkaline layer was separated, diluted, acidified with hydrochloric acid, and redigested with sodium hydrogen carbonate solution, after which it was boiled (to coagulate inorganic matter), cooled, and filtered. Acidification of the filtrate

TABLE 2.

Mixture	*ortho*-Isomer (%)	*meta*-Isomer (%)	*para*-Isomer (%)	*para*-Isomer by infrared analysis (%)
3	11·9	48·2	39·9	36·0
4	11·7	49·5	38·8	44·0
Mean	11·8	48·8	39·3	40·0
Synthetic mixture {Known	10·1	60·5	29·3	29·3
Synthetic mixture {Found	11·5	56·9	31·6	28·0

TABLE 3.

Experiment no.:	7	8	9	10
Free *p*-nitrobenzoic acid (g.) ...	2·05	2·22	2·02	1·99
Biaryls (g.)	2·06	1·97	2·10	1·97
Residue (g.)	0·094	0·084	0·079	0·106

gave a precipitate, which was extracted with ether and then with chloroform to remove all the 4′-nitrobiphenyl-4-carboxylic acid. Evaporation of the combined extracts left a light-brown solid, which was dried *in vacuo* and then dissolved in a large excess of ether to which was added an excess of ethereal diazomethane. After 14 hr. at room temperature the solution was concentrated to small bulk (10—15 ml.) and then distilled. Two main fractions were collected: (*a*) b. p. 76—80°/12 mm. and (*b*) b. p. 80—100°/0·05 mm. Fraction (*a*) consisted of methyl benzoate. Fraction (*b*) contained the biaryls, the final traces of which had to be removed from the stem of the distillation flask by means of a small flame. The solid which came over at this stage was identified as methyl 4′-nitrobiphenyl-4-carboxylate, m. p. 186—188° (from acetone) (mixed m. p. and infrared spectrum). There was a small residue which did not distil at 150°/0·05 mm. The organic layer from the hydrolysis was dried ($CaCl_2$) and evaporated, and the residue was chromatographed as described above for the corresponding reaction with benzoyl peroxide. The product was an orange-red tar (1·5 g.), from which no solid could be obtained. The results obtained in experiments 7—10 are given in Table 3.

Determination of the Isomer Ratios in the Methyl Nitrobiphenylcarboxylates derived from the p-*Nitrophenylation of Benzotrichloride.*—Examination of the spectra of the three isomeric 4-nitro-esters as Nujol mulls suggested the following wavelengths for analytical purposes: *ortho* 701·3 cm.$^{-1}$, 800·0 cm.$^{-1}$; *meta* 763·4 cm.$^{-1}$, 843·7 cm.$^{-1}$; *para* 778·1 cm.$^{-1}$. Dimethylormamide was used as the solvent. The spectra of the mixtures of nitro-esters did not reveal the presence of any bands other than those known to be due to the isomers. Examination of the spectra of mixtures of known composition showed that the concentration of the *ortho*-isomer in the reaction mixtures could not have been greater than 3%, and that difficulties would be encountered in the analysis of the content of the *meta*-isomer. Accordingly, determinations were made of the content of the *para*-isomer, as previously carried out for the methyl biphenylcarboxylates, and the content of the *meta*-isomer was calculated by difference on the assumpton that 3% of the *ortho*-isomer was present. In this manner the values obtained for the *para*-isomer formed in experiments 7, 8, 9, and 10 were found to be 34·2, 29·5, 35·2, and 31·5% (mean 32·5%). These results are considered to be accurate only to ±4%. The isomer ratios resulting from the attack of *p*-nitrophenyl radicals on benzotrichloride may therefore be represented as follows: *ortho* ⩾3%; *meta* 64·5% (±4); *para* 32·5% (±4).

The Reaction between Benzoyl Peroxide and Benzotrifluoride.—Reactions 11—14 were carried out with benzoyl peroxide (6 g.) in benzotrifluoride (200 g.) at 80° for 72 hr. as described above for the reactions with benzotrichloride. Free benzoic acid was removed by extraction with aqueous sodium hydrogen carbonate as previously described, and the excess of benzotrifluoride was removed by distillation at atmospheric pressure. The residue was boiled under reflux with 10% aqueous sodium hydroxide (100 ml.) for 14 hr. and extracted as previously described. The alkaline layer was acidified and the liberated acid was extracted with ether. The organic layer from the hydrolysis was dried (Na_2SO_4) and after removal of benzene (wash-liquid) at

XUM

atmospheric pressure the residue was distilled to give three fractions: (*a*) b. p. 20°/15 mm.; (*b*) b. p. 102—120°/10 mm. (*ca.* 4·5 g.); and (*c*) b. p. 70—90°/0·05 mm. (*ca.* 1·5 g.). Fraction (*a*) was benzotrifluoride. Fraction (*b*) contained the trifluoromethylbiphenyls. Fraction (*c*) solidified to a glass which was dissolved in benzene and chromatographed. Only a small

TABLE 4.

Experiment no.:	11	12	13	14
Free benzoic acid (g.)	0·74	0·65	0·71	0·67
Benzoic acid from esters (g.)	0·20	0·22	0·17	0·24
Trifluoromethylbiphenyls (g.)	4·605	4·617	4·801	4·129
Higher-boiling fraction (g.)	1·511	1·359	0·969	1·658
Residue (g.)	1·004	0·833	1·164	1·145

TABLE 5.

Mixture		*ortho*-Isomer (%)	*meta*-Isomer (%)	*para*-Isomer (%)
11		32·2	37·6	30·2
12		36·0	37·4	26·6
13		36·4	35·3	28·3
14		31·0	37·7	31·3
Mean		33·9	37·0	29·1
Synthetic mixture	Known	40·3	40·9	18·8
	Found	37·2	42·2	20·6

TABLE 6.

Mixture	*ortho*-Isomer (%)	*meta*-Isomer (%)	*para*-Isomer (%)
12	29·4	41·2	29·4
13	29·4	41·0	29·6
Mean	29·4	41·1	29·5

quantity of solid (0·1 g.; m. p. 50—70°) was, however, recovered. The products obtained in these reactions are given in Table 4. The weight of benzoic acid formed by the hydrolysis of esters is included in this Table since, unlike benzotrichloride, benzotrifluoride is not readily hydrolysed under the conditions employed.

Determination of the Isomer Ratios in the Trifluoromethylbiphenyls obtained from the Phenylation of Benzotrifluoride.—(a) *Infrared method.* 2-Trifluoromethylbiphenyl was examined as a liquid film and the 3- and 4-isomerides as Nujol mulls. The following wavelengths were chosen for analytical purposes: *meta* 819·7 cm.$^{-1}$, 809·8 cm.$^{-1}$; *para* 842·2 cm.$^{-1}$. Nitromethane was used as solvent and analyses were carried out on the products of the four reactions and on a synthetic mixture of known composition. The results are given in Table 5.

(b) *Gas–liquid chromatographic method.* For details see above. The results are given in Table 6. The presence of a fourth component of unknown identity in these mixtures was revealed by the chromatograms, which contained a small extra peak. This is probably the explanation of the slight discrepancy between the results of the infrared and gas–liquid chromatographic analyses. The latter method is the more reliable, since each isomer is estimated separately and the result is therefore unaffected by the presence of impurities. In the infrared method, however, the amount of *ortho*-isomer is obtained by difference and the result may therefore be high, as it also includes the impurities. For this reason, the results obtained by the chromatographic method are accepted as the more accurate.

DISCUSSION

Dannley and Sternfeld [1] attributed the complete absence of substitution at the *ortho*-position with reference to the trichloromethyl group in the arylation of benzotrichloride to steric hindrance. A similar argument was put forward to account for the low yield (18%) of the *ortho*-isomer in the phenylation of benzotrifluoride. It has been shown that in the phenylation of t-butylbenzene the *ortho*-isomer constitutes some 24% of the mixture of t-butylbiphenyls.[4] In view of the comparative sizes of the groups ·CMe_3 and ·CCl_3, it would seem that the total absence of substitution at the *ortho*-position in benzotrichloride on steric grounds alone would be most improbable and the value now reported of 12% *ortho*-substitution appears more reasonable. The existence and concentration of this

isomer in the product of the phenylation of benzotrichloride was established by means of gas–liquid chromatography on the mixture of isomeric methyl biphenylcarboxylates obtained from the trichloromethylbiphenyls by hydrolysis and esterification. The concentration of peroxide and of benzotrichloride employed (0·025 : 1) ensures that very little of the biphenylcarboxylic acids is formed by phenylation of the free benzoic acid resulting from the decomposition of the peroxide. The low yield reported for the *ortho*-

TABLE 7. *The arylation of benzotrihalides.*

X in $Ph{\cdot}CX_3$	Radica	Ratio of isomers (%) *ortho*	*meta*	*para*	Method of analysis	Reference
F	Ph·	18	40	42	IR	Dannley & Sternfeld [1]
F	Ph·	20	40	40	IR	Rondestvedt & Blanchard [2]
F	Ph·	29·4	41·1	29·5	GLC	This work
Cl	Ph·	0	60	40	IR	Dannley & Sternfeld [1]
Cl	Ph·	12	49	39	GLC	This work
Cl	p-$NO_2{\cdot}C_6H_4$·	0	100	0	IR	Dannley & Sternfeld [1]
Cl	p-$NO_2{\cdot}C_6H_4$·	$\gtrsim 3$	64·5 ± 4	32·5 ± 4	IR	This work

isomer in the phenylation of benzotrifluoride by both Dannley and Sternfeld [1] (18%) and Rondestvedt and Blanchard [2] (20%), also attributed to steric hindrance, is again not in keeping with the values reported for *ortho*-substitution in t-butylbenzene [4] (24%), isopropylbenzene [5] (31%), and toluene [5] (66%). The higher figure now reported for phenylation at the *ortho*-position in benzotrifluoride, namely, 29·4%, seems to be more realistic. This figure was obtained by gas–liquid chromatography and is supported by the results of infrared analysis.

The extent of substitution at the *meta*-position in the arylation of benzotrichloride would be expected to be greater for *p*-nitrophenylation than for phenylation, as a result of the electrophilic character of the *p*-nitrophenyl radical. This increase was observed by Dannley and Sternfeld [1] and is confirmed in the present work. However, the exclusive *meta*-substitution reported by Dannley and Sternfeld [1] appears highly improbable, and the existence of appreciable simultaneous substitution at the *para*-position has now been established beyond doubt by the isolation of methyl 4′-nitrobiphenyl-4-carboxylate by hydrolysis and methylation of the product obtained from the *p*-nitrophenylation of benzotrichloride. These results are summarised in Table 7.

Side-chain attack in the arylation of benzotrichloride is important in phenylation (66% by weight of the total binuclear products), but appears to be absent in *p*-nitrophenylation. This is in agreement with earlier observations on the *p*-nitrophenylation of toluene.[12] No identifiable products were obtained from reaction at the side-chain in the phenylation of benzotrifluoride. Attempts to prepare 1,1,2,2-tetrafluorodiphenylethane gave, instead, 1,2-diphenyl-1,2-difluoroethylene, which might be susceptible to polymerisation. This may in fact account for the resinous material formed in the phenylation of benzotrifluoride. Dannley and Sternfeld [1] have, however, reported the isolation of very small quantities of difluorodiphenylmethane and fluorobenzene from the products of the phenylation of benzotrifluoride. Difluorodiphenylmethane in fact may be present in the eluates containing the *ortho*- and *meta*-phenylbenzotrifluorides reported in the present work, because a small additional peak was observed in the gas–liquid chromatogram.

Partial rate factors for the phenylation of benzotrifluoride may be calculated from the isomer ratios reported in this paper coupled with the value for ${}^{PhCF_3}_{PhH}K = 0{\cdot}99$ reported by Rondestvedt and Blanchard.[2] Thus:

$$F_o = 3 \times 0{\cdot}99 \times 0{\cdot}294 = 0{\cdot}87$$
$$F_m = 3 \times 0{\cdot}99 \times 0{\cdot}411 = 1{\cdot}21$$
$$F_p = 6 \times 0{\cdot}99 \times 0{\cdot}295 = 1{\cdot}76$$

[12] Augood and Williams, *Chem. Rev.*, 1957, **57**, 171.

XUM

On the other hand, partial rate factors for the phenylation of benzotrichloride are not available because the high incidence of side-chain attack renders an accurate determination of the rate ratio very difficult.

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111. *Homolytic Aromatic Substitution. Part XXII.* The Esters formed in the Reaction of Benzoyl Peroxide with Aromatic Solvents.*

By D. I. DAVIES, D. H. HEY, and GARETH H. WILLIAMS.

When benzoyl peroxide is allowed to decompose in aromatic solvents, a little phenyl benzoate is formed together with the esters resulting from the attack of a benzoyloxy-radical on the solvent. The lactone of 2′-hydroxybiphenyl-2-carboxylic acid is also a minor product in the reaction of benzoyl peroxide with aromatic solvents.

GELISSEN and HERMANS [1,2] studied the reaction of benzoyl peroxide with benzene and found that phenyl benzoate was a minor product. They attributed its formation to the substitution of a benzoyloxy-group for a hydrogen atom in benzene. Böeseken and Hermans [3] later suggested that phenyl benzoate could also arise by the loss of a molecule of carbon dioxide from a molecule of the peroxide, a possibility also envisaged by Hey and Waters,[4] thus: $(Ph{\cdot}CO{\cdot}O)_2 \longrightarrow CO_2 + Ph{\cdot}CO_2Ph$. Nozaki and Bartlett [5] studied the kinetics of the decomposition of benzoyl peroxide in organic solvents and considered that the formation of phenyl benzoate could occur either (*a*) by reaction between two benzoyloxy-radicals with loss of carbon dioxide, or (*b*) by an induced decomposition of benzoyl peroxide by means of a benzoyloxy-radical:

(*a*) $(Ph{\cdot}CO{\cdot}O)_2 \longrightarrow 2Ph{\cdot}CO{\cdot}O{\cdot}$

$2Ph{\cdot}CO{\cdot}O{\cdot} \longrightarrow CO_2 + Ph{\cdot}CO_2Ph$

(*b*) $Ph{\cdot}CO{\cdot}O{\cdot} + (Ph{\cdot}CO{\cdot}O)_2 \longrightarrow CO_2 + Ph{\cdot}CO_2Ph + Ph{\cdot}CO{\cdot}O{\cdot}$

The reaction of benzoyl peroxide and of substituted benzoyl peroxides with benzene was further investigated by Lynch and Pausacker,[6,7] who attempted to write balanced equations for these reactions. On the basis of these equations they concluded that phenyl benzoate is formed as a result of an intramolecular loss of carbon dioxide from the peroxide and not by the substitution of a benzoyloxy-radical for a hydrogen atom in benzene. If the mechanism postulated by Lynch and Pausacker [6] for the formation of phenyl benzoate in the reaction of benzoyl peroxide with benzene is correct, then when a substituted benzoyl peroxide reacts with benzene the only ester formed should be that resulting from the intramolecular loss of carbon dioxide from the peroxide, *e.g.*, in the reaction of *p*-chlorobenzoyl peroxide with benzene the only ester expected would be *p*-chlorophenyl *p*-chlorobenzoate. Hydrolysis of the ester would give a single phenol which would be uncontaminated with phenol itself. In his analysis of the phenolic fraction obtained in

* Part XXI, preceding paper.

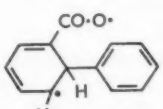
[1] Gelissen and Hermans, *Ber.*, 1925, **58**, 285.
[2] Gelissen and Hermans, *Ber.*, 1925, **58**, 984.
[3] Böeseken and Hermans, *Annalen*, 1935, **519**, 133.
[4] Hey and Waters, *Chem. Rev.*, 1937, **21**, 169.
[5] Nozaki and Bartlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1686.
[6] Lynch and Pausacker, *Austral. J. Chem.*, 1957, **10**, 40.
[7] Pausacker, *Austral. J. Chem.*, 1957, **10**, 49.

XUM

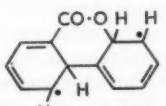
this experiment, Pausacker [7] found that the results were not consistent with the hypothesis that the ester was derived entirely from the peroxide, but he did not comment on this fact. It therefore appeared desirable to investigate the extent to which esters are formed by processes (*a*) and (*b*) above, rather than by the substitution of an aroyloxy-radical for a hydrogen atom of the solvent.

In a re-investigation of the reactions of benzoyl peroxide with chlorobenzene and with biphenyl it is now shown that both types of ester are formed. The products were found to contain mixtures of phenol and chlorophenols, and of phenol and hydroxybiphenyls respectively. The yield of phenyl benzoate is greater with the less reactive solvent (chlorobenzene) than with the more reactive solvent (biphenyl), which supports the mechanism of an induced decomposition, since this would be of less importance in the more reactive solvent. Further, the yield of biphenylyl benzoates from the reaction of benzoyl peroxide with biphenyl is greater than the yield of chlorophenyl benzoates from the reaction with chlorobenzene. This is expected, because in the more reactive solvent (biphenyl) the benzoyloxy-radical is more likely to react with the solvent before decarboxylation.

When the esters formed in the reactions of benzoyl peroxide with chlorobenzene and with biphenyl were hydrolysed, the phenolic fraction was found to contain some high-boiling material, a component of which was found to be the lactone of 2′-hydroxybiphenyl-2-carboxylic acid. This lactone may result from loss of carbon dioxide from a molecule of



(I)



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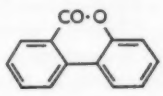

(III)

benzoyl peroxide, which can give a phenyl radical and a benzoyloxy-radical. These two radicals may react to give an intermediate (I), which subsequently becomes (II), which in turn can undergo dehydrogenation, either by the solvent or by another radical, to give the lactone (III). These reactions can be envisaged as taking place within a solvent cage. The intermediates (I) and (II) can, of course, be written in several canonical forms.

A somewhat similar mechanism for the formation of the lactone can be formulated by the attack of a phenyl radical at an *ortho*-position in a molecule of benzoyl peroxide (cf. DeTar and Weis,[8] and Walling and Savas [9]). The appearance of the lactone in the phenolic fraction is due to its insolubility in sodium hydrogen carbonate solution.

Experimental

Reagents.—Benzoyl peroxide and chlorobenzene were purified as in Part II,[10] and biphenyl as in Part V.[11] The lactone, m. p. 93·5°, of 2′-hydroxybiphenyl-2-carboxylic acid was prepared from the diazonium sulphate of anthranilic acid and phenol by the method of Graebe and Schestakow.[12]

Reaction of Benzoyl Peroxide with Chlorobenzene.—Two reactions were carried out. In reaction (I), benzoyl peroxide (25 g.) was allowed to decompose in chlorobenzene (50 g.) at 80° (thermostat) for 72 hr. In reaction (II), benzoyl peroxide (24 g.) in chlorobenzene (800 g.) was used. When the reactions were complete, the free acid was extracted with saturated aqueous sodium hydrogen carbonate, and then the excess of solvent was removed by distillation. The residue was hydrolysed for 24 hr. with boiling 2N-aqueous sodium hydroxide (200 ml.), and the "ester" acid and the phenols were isolated by standard methods. The biaryls in the neutral fraction were not isolated. The products isolated are shown in Table 1.

Fraction (*a*) was shown to consist of a mixture of phenol and chlorophenols by a comparison

[8] DeTar and Weis, *J. Amer. Chem. Soc.*, 1956, **78**, 4296.
[9] Walling and Savas, *J. Amer. Chem. Soc.*, 1960, **82**, 1738.
[10] Augood, Hey, and Williams, *J.*, 1952, 2094.
[11] Cadogan, Hey, and Williams, *J.*, 1954, 794.
[12] Graebe and Schestakow, *Annalen*, 1895, **284**, 306.

of its infrared spectrum with those of authentic specimens of phenol and the three chlorophenols, and the percentage compositions shown in Table 2 were obtained by element analyses.

In reaction (I), fraction (*b*) was obtained as a yellowish-white semi-solid. Successive recrystallisations from light petroleum (b. p. 80—100°) gave 2′-hydroxybiphenyl-2-carboxylic acid lactone, m. p. 91·5°, which was undepressed on admixture with an authentic specimen.[12] The two specimens had identical infrared spectra. The presence of the lactone in the phenolic fraction (*b*) of reaction (II) was shown by the presence of an absorption band at 5·8 μ. From both the free acid and the " ester " acid in reaction (I) it was possible to isolate, by fractional crystallisation, biphenyl-4-carboxylic acid (0·80 g., and 0·15 g. respectively), m. p. 223·5—224·5° (Found: C, 78·5; H, 5·4. Calc. for $C_{13}H_{10}O_2$: C, 78·8; H, 5·1%).

TABLE 1. *Yields of free acid and of the products of hydrolysis from the reaction of benzoyl peroxide with chlorobenzene.*

Reaction no.	(I)	(II)
Free acid (g.)	7·71	5·98
" Ester " acid (g.)	1·26	0·72
Phenolic fraction (*a*), b. p. 80—100°/20 mm. (g.)	0·164	0·184
Phenolic fraction (*b*), b. p. 120—130°/0·1 mm. (g.)	0·550	0·136
Non-volatile residue (g.)	0·057	0·028

TABLE 2. *Composition of phenolic fraction* (a).

Reaction no.	(I)	(II)
Chlorine (%)	11	15·2
Chlorophenols (%)	40	55
Phenol (%)	60	45

Reaction of Benzoyl Peroxide with Biphenyl.—In reaction (III), benzoyl peroxide (25 g.) was allowed to decompose in biphenyl (68·5 g.) at 80° (thermostat) for 72 hr. In reaction (IV), benzoyl peroxide (24 g.) in biphenyl (800 g.) was used. The products were worked up as described above for the reactions with chlorobenzene. In reaction (III), benzene (250 ml.) was added to the reaction mixture before the extraction of the free benzoic acid. The biaryls were not isolated. Table 3 gives the quantities of free acid and the products of hydrolysis obtained.

The phenolic fraction (*a*) was phenol, m. p. 43° (correct infrared spectrum). The phenolic fraction (*b*), which partly distilled and partly sublimed, was collected as a solid and was shown to consist mainly of hydroxybiphenyls by a comparison of its infrared spectrum with that of an authentic mixture of the isomeric hydroxybiphenyls. A weak band was observed

TABLE 3. *Yield of free acid and of the products of hydrolysis from the reaction of benzoyl peroxide with biphenyl.*

Reaction no.	(III)	(IV)
Free acid (g.)	9·67	Not estimated
" Ester " acid (g.)	1·82	1·70
Phenolic fraction (*a*), b. p. *ca.* 85°/20 mm. (g.)	0·045	0·021
Phenolic fraction (*b*), b. p. 90—130°/0·1 mm. (g.)	0·872	0·953
Non-volatile residue (g.)	0·137	0·100

in the spectrum at 5·8 μ, indicating the presence of 2′-hydroxybiphenyl-2-carboxylic acid lactone. This fraction, from reaction (III), was further distilled at 0·1 mm., to give: (i) at bath-temp. 100—180°, 0·25 g.; (ii) at bath-temp. 180—240°, 0·50 g.; and (iii) at bath. temp. 240—300°, 0·12 g. Fraction (i) solidified, and recrystallisation from light petroleum (b. p. 80—100°) gave 2-hydroxybiphenyl, needles, m. p. and mixed m. p. 56° (Found: C, 84·7; H, 5·8. Calc. for $C_{12}H_{10}O$: C, 84·7; H, 5·9%). Fraction (ii), on the evidence of its infrared spectrum, consisted of a mixture of 3- and 4-hydroxybiphenyl, and fractional crystallisation from light petroleum (b. p. 80—100°) gave 4-hydroxybiphenyl in needles, m. p. and mixed m. p. 165°. Fraction (iii) showed a strong absorption band at 5·8 μ. Several recrystallisations from light petroleum (b. p. 80—100°) gave the lactone in needles, m. p. and mixed m. p. 92·5° (Found: C, 80·0; H, 4·45. Calc. for $C_{13}H_8O_2$: C, 79·6; H, 4·1%). Similar results were obtained for the products from reaction (IV).

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112. *Homolytic Aromatic Substitution. Part XXIII.* A Redetermination of the Relative Rate of Phenylation of Nitrobenzene.*

By D. H. Hey, S. Orman, and Gareth H. Williams.

With the aid of improved experimental techniques the relative rate of phenylation of nitrobenzene has been redetermined. The value for $^{Ph\cdot NO_2}_{PhH}K$ reported in 1952 as 4·0 was regarded as a *maximum* value. The redetermined value is 2·94. The wide use of nitrobenzene as a standard substrate in the competitive method for measuring the relative rates of arylation reactions has necessitated a revaluation of a number of relative rates and partial rate factors. The corrections, which amount to small reductions in the absolute values, do not invalidate any of the theoretical deductions made on the basis of the earlier figures.

The determination of the relative rate of phenylation of nitrobenzene, by means of competitive experiments in which benzoyl peroxide was allowed to decompose in a large excess of an equimolar mixture of benzene and nitrobenzene, was reported in Part II.[1] The value obtained for the relative rate, $^{Ph\cdot NO_2}_{PhH}K$, was 4·0. This result was, however, accepted as a *maximum* value, since the results of a number of experimental determinations revealed that the measurement of the relative rate was uniquely subject to an error due to loss of the rather volatile biphenyl in the nitrobenzene fraction during the removal of solvents by distillation. At that time, it was not possible completely to eliminate or correct for this error, and the value obtained for $^{Ph\cdot NO_2}_{PhH}K$ was therefore accepted with these reservations, as the possible error was not considered to be serious and the order of magnitude of the result was undoubtedly correct. More recently, however, it has become clear that a more accurate knowledge of this relative rate is desirable, partly because nitrobenzene has been used as a sub-standard for the determination of the relative rates of phenylation of a large number of other compounds and partly for purposes of comparison with the relative rates of arylation of nitrobenzene and other substances with aryl radicals other than phenyl. A more accurate determination of $^{Ph\cdot NO_2}_{PhH}K$ was therefore called for and, as a result of the development of more refined analytical techniques (particularly that of gas–liquid chromatography), this has become possible. The results of this redetermination are now reported, and their implications discussed.

Experimental

Benzoyl peroxide, benzene, and nitrobenzene were purified as described in Part II.[1]

Determination of $^{Ph\cdot NO_2}_{PhH}K$.—In experiments 1—4 benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of benzene and nitrobenzene at 80° (thermostat) for 72 hr. The products of these reactions were isolated by the following procedure, which differs appreciably from that described in Part II.[1]

(i) The reaction mixture was extracted with saturated aqueous sodium hydrogen carbonate (5 × 50 ml.) to remove free benzoic acid, and then washed with water (2 × 25 ml.). The combined aqueous extracts were washed with ether (3 × 30 ml.), and the ethereal washings added to the reaction mixture, which was then dried ($MgSO_4$). Benzoic acid (m. p. 122°) was obtained from the alkaline extracts by acidification with hydrochloric acid and extraction with ether (4 × 30 ml.). The ethereal extracts were dried ($MgSO_4$) and the ether removed by evaporation.

(ii) Benzene was removed from the reaction mixture after treatment as described above, by slow distillation through a 40 cm. helix-packed column. The bulk of the nitrobenzene was then removed by fractional distillation under reduced pressure (b. p. 140°/105 mm.). The distillate was redistilled through the column under the same conditions, and the final fraction

* Part XXII, preceding paper.

[1] Augood, Hey, and Williams, *J.*, 1952, 2094.

(~3 ml.) combined with the residue from the first distillation (~15 ml.). The distillate was again redistilled, and the final fraction (~5 ml.) retained as a pre-forerun. The column and still-head were washed with ether, the washings were combined with the residue, and the ether was removed by evaporation.

(iii) The residue from (ii) was refluxed with 2N-aqueous sodium hydroxide solution (100 ml.) for 24 hr. in order to hydrolyse the esters present. The resulting dark mixture was filtered through toughened paper and then extracted as follows: (*a*) The mixture was extracted with benzene (3 × 30 ml.) and the extracts were combined (portion X). (*b*) The aqueous layer was washed with benzene (30 ml.; portion Y). (*c*) Portion X was washed with 2N-sodium hydroxide (2 × 25 ml.). (*d*) The combined aqueous washings were shaken with the benzene portion Y. (*e*) All the benzene extracts were combined and washed with 3N-hydrochloric acid (25 ml. portions) until the washings were colourless, in order to remove any basic material formed by reduction of nitrobenzene. The benzene solution was then washed with water (2 × 25 ml.) and dried (Na_2SO_4). (*f*) The aqueous extracts obtained in stages (*a*)—(*d*) were combined, warmed, acidified with hydrochloric acid, and neutralised with an excess of solid sodium hydrogen carbonate. The mixture was boiled, cooled in ice, and filtered to remove silicic acid formed as sodium silicate by solution of the glass of the flask in sodium hydroxide during the hydrolysis stage. The residue was digested with sodium hydrogen carbonate solution (100 ml.) and filtered. The combined filtrates were extracted with ether (3 × 30 ml.) to remove phenols formed by the hydrolysis of the esters. The aqueous layer was acidified with hydrochloric acid, and the precipitated benzoic acid removed by extraction with ether (4 × 30 ml.). The resulting ethereal solution was dried ($MgSO_4$) and the ether removed by evaporation, giving benzoic acid (m. p. 122° after crystallisation).

(iv) The dried benzene solution obtained in (iii*e*) was reduced in volume by distillation through the helix-packed column, the last traces of benzene (~15 ml.) being removed at 150 mm. A mixture of anhydrous ether and dry " AnalaR " acetone was used to wash the column and accessories, and these washings were used for the transfer of the residue in the next stage.

(v) The residue (~18 ml.) was divided into two portions (A and B), which were quantitatively transferred, with acetone wash-liquid, to small, weighed distilling flasks (~15 ml. capacity). The wash-liquid was removed by careful distillation at atmospheric pressure. The pressure was then reduced to 0·01 mm. and the bath-temperature raised gradually to 55° during 36 hr. During this period the forerun (b. p. 17—35°/0·01 mm.) was collected in a cooled, weighed receiver. The bath-temperature was then slowly raised to 250° and the biaryl fraction (b. p. 40—115°/0·01 mm.) collected in a second cooled, weighed receiver.

Analysis of products. The eight biaryl fractions were analysed for nitrobiphenyls by titration with titanous sulphate as described in Part XVIII,[2] and the foreruns and pre-foreruns for nitrobenzene by the same method. Tests with appropriate synthetic mixtures of known composition showed that both nitrobenzene and nitrobiaryls could be estimated to ±1%.

These analytical results were confirmed by analysis of the foreruns, pre-foreruns, and biaryl fractions by gas–liquid chromatography. The instrument used was a Perkin–Elmer model 116 vapour fractometer. The stationary phase was Apiezon " L " grease supported on Celite, and contained in a 1 m. column, and the carrier gas was nitrogen. The pre-foreruns were found to consist entirely of nitrobenzene, so that all the biaryls formed were contained in the foreruns and biaryl fractions. The foreruns consisted largely of nitrobenzene, but contained a little biphenyl, the amount of which could be estimated from the chromatograms. The compositions of the foreruns, as determined titrimetrically and chromatographically, were in close agreement (±1%).

Chromatography of synthetic mixtures of 2-, 3-, and 4-nitrobiphenyl showed that complete separation of the peaks corresponding to the 3- and 4-isomers could not be effected, and conditions were therefore chosen such that these two isomers emerged together and were shown on the chromatogram as a single peak. The biaryl fractions were then chromatographed under these conditions (column temperature 330°; detector block temperature 202°; detector voltage 6 v; carrier gas flow rate 10 ml. $min.^{-1}$; gas pressure 0·25 kg. $cm.^{-2}$). The composition of these mixtures of biphenyl and 2-, 3-, and 4-nitrobiphenyl could not be obtained directly by measurement of the areas of the peaks corresponding to these components since, as the detector unit of the instrument is a catharometer, these areas depend, not only on the amounts

[2] Hey, Moulden, and Williams, *J.*, 1960, 3769.

XUM

of the various components present, but also on the thermal conductivities of their vapours. Calibration was therefore necessary, and was effected as follows.

A mixture of 2-, 3-, and 4-nitrobiphenyl was prepared which contained these compounds in as nearly as possible the proportions in which they are formed by the phenylation of nitrobenzene with benzoyl peroxide [3,4] (2-nitrobiphenyl 58%, 3-nitrobiphenyl 10%, 4-nitrobiphenyl, 32%). Weighed portions of this homogeneous mixture were added to weighed amounts of biphenyl to give a range of mixtures which simulated the biaryl fractions and contained from 10 to 17% of biphenyl. These mixtures were chromatographed, and a graph drawn of the areas of the biphenyl peaks expressed as percentages of the sum of the areas of all the peaks against the known percentages of biphenyl in the mixture. This graph, which was a straight line, enabled the composition of the unknown mixtures (biaryl fractions) to be obtained from the peak areas in their chromatograms by interpolation. Very small peaks corresponding to nitrobenzene were observed in the chromatograms of all the biaryl fractions, and from their areas it was calculated that the amount of nitrobenzene present in these mixtures was not more than 0·2%. The results obtained in experiments 1—4 are summarised in Table 1.

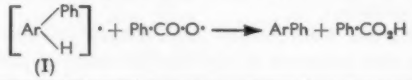
TABLE 1.

Expts.	1		2		3		4	
Portions	A	B	A	B	A	B	A	B
Biaryl fraction (g.)	1·770	1·650	1·493	1·770	1·748	1·492	1·685	1·725
Nitrobiphenyls (%) in biaryl fractions:								
(*a*) by titration	84·04	87·00	86·70	85·19	85·43	87·24	85·22	85·81
(*b*) by chromatography	84·95	86·60	87·65	85·03	86·80	87·07	85·00	86·25
Forerun (g.)	2·866	4·572	2·879	3·957	5·619	4·934	4·710	5·957
Nitrobenzene (%) in forerun (mean of determinations by titration and chromatography)	96·49	95·85	95·32	96·96	97·21	96·07	97·83	97·31
Biphenyl (g.) in forerun	0·101	0·190	0·135	0·120	0·157	0·194	0·102	0·160
Corr. wt. of biaryl fractions (g.)	1·871	1·840	1·628	1·890	1·905	1·686	1·787	1·885
Nitrobiphenyls (corr. %):								
(*a*) by titration	79·6	78·0	79·6	79·8	78·4	77·2	80·4	78·5
(*b*) by chromatography	80·4	76·7	80·4	79·5	79·7	77·0	80·2	78·9
(*c*) mean	80·0	77·9	80·0	79·7	79·1	77·1	80·3	78·7
$^{Ph\cdot NO_2}_{PhH}K$	3·10	2·73	3·10	3·04	2·94	2·61	3·15	2·86
Residue (g.)	0·120	0·139	0·139	0·161	0·135	0·102	0·143	0·148
Free benzoic acid (g.)	2·940		2·921		2·961		2·904	
Benzoic acid from hydrolysis of esters (g.)	0·416		0·469		0·448		0·440	
Benzoyl peroxide accounted for (%) (excluding residue)	95·4		93·8		95·0		94·9	

Hence $^{Ph\cdot NO_2}_{PhH}K = 2·94$.

DISCUSSION

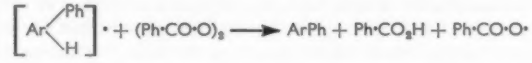
Stoicheiometry.—The rate-determining stage of the process of replacement of hydrogen attached to an aromatic nucleus by a phenyl radical has been shown (cf. Part XVII [5]) to be the addition of the phenyl radical to the nucleus of the substrate molecule to give an arylcyclohexadienyl radical, or " σ-complex " (I). This process is thought to be followed by the removal of a hydrogen atom from (I) by another radical or other oxidising agent, leaving the biaryl product. It has been considered that the most likely oxidising agent is the benzoyloxy-radical, which may be present, together with the σ-complex, in a " solvent-cage." [6] The oxidation process is then represented as follows:



(I)

[3] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.
[4] Chang, Hey, and Williams, *J.*, 1958, 1885.
[5] Chang, Hey, and Williams, *J.*, 1959, 1871.
[6] Huisgen and Sorge, *Annalen*, 1950, **566**, 162; Waters, *Ann. Reports*, 1952, **49**, 110.

In addition, Foster and Williams (unpublished observations) have shown that benzoyl peroxide molecules also contribute appreciably to the oxidation process, and the stoicheiometry of this reaction is represented by the equation:



The benzoyloxy-radicals formed in such a process may react further by decarboxylation to give phenyl radicals, with arylcyclohexadienyl radicals as suggested above, or with molecules of the substrate to give, ultimately, phenolic esters. The formation of these esters (benzoyloxylation) is a reaction of homolytic aromatic substitution which always accompanies arylation when aroyl peroxides and related substances are used as radical sources. With benzene and its simple derivatives it is generally a minor contribution to the total reaction, and probably proceeds by a mechanism involving, as its first stage, the formation of σ-complexes similar to (I), which then become oxidised by analogous means.

If the foregoing is a correct representation of the total reaction, it follows that the molar yield of benzoic acid should be equal to the sum of the molar yields of all the products of substitution. If, however, other reactions of the various σ-complexes, which do not involve benzoyloxy-radicals or benzoyl peroxide, occur, then the yield of benzoic acid should be less than the sum of the yields of the substitution products. Such processes, in which two arylcyclohexadienyl radicals interact to give either a biaryl and a dihydrobiaryl, or a tetrahydroquaterphenyl derivative, have been shown to take place when benzoyl peroxide is allowed to decompose in very dilute solution in benzene under a nitrogen atmosphere.[7] The relevant data for the reactions at present under consideration are given in Table 2. If the small residues formed are considered to be substitution products, the

TABLE 2.

Expt.	1	2	3	4
Free acid (mole)	0·0241	0·0239	0·0243	0·0238
Acid from esters (mole)	0·0034	0·0038	0·0037	0·0036
Nitrobiaryls (mole)	0·0147	0·0141	0·0141	0·0147
Biphenyl (mole)	0·0051	0·0046	0·0051	0·0049
Residue (mole, calc. on M = 300)	0·0009	0·0010	0·0008	0·0010
Total substitution products (mole)	0·0241	0·0235	0·0237	0·0242
Ratio of molar yields (free acid/substitution products)...	1·000	1·017	1·025	0·9835
Peroxide accounted for (%) (including residue)	97·1	95·8	96·6	96·8

Mean ratio of molar yields = 1·006.

results show that the balance of the yields of the two groups of products is in excellent agreement with the mechanism involving oxidation by benzoyloxy-radicals and benzoyl peroxide only. If these residues are omitted from the calculation, the yield of benzoic acid exceeds the combined yield of the substitution products. In either event, the results afford no evidence for dimerisation or disproportionation involving two arylcyclohexadienyl radicals, and it may therefore be concluded that such processes do not contribute appreciably to this reaction when it is carried out under the conditions described in the foregoing experimental section.

Relative Rates and Partial Rate Factors for Phenylation.—In previous papers in this series the determination was reported of the relative rates of phenylation of a number of benzene derivatives. Most of these determinations were conducted by means of competitive experiments in which nitrobenzene was used as the standard competing solvent.

[7] De Tar and Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4742.

XUM

Thus, the relative rate determined, for a solvent PhX, was ${}^{PhX}_{Ph\cdot NO_2}K$, and the rate of phenylation relative to benzene, ${}^{PhX}_{PhH}K$, was obtained from this ratio by multiplication by the relative rate of phenylation of nitrobenzene, since

$$ {}^{PhX}_{PhH}K = {}^{PhX}_{Ph\cdot NO_2}K \times {}^{Ph\cdot NO_2}_{PhH}K $$

These determinations were not, in general, subject to the errors discussed above in connection with the determination of ${}^{Ph\cdot NO_2}_{PhH}K$, since all the biaryls $X\cdot C_6H_4\cdot C_6H_5$ are considerably less volatile than biphenyl, and hence were not lost during the distillation of the solvents. In most cases, this was made clear by the analysis of foreruns and pre-foreruns. Nevertheless, the derived relative rates ${}^{PhX}_{PhH}K$ previously reported must now be corrected, by using the new value of 2·94 for ${}^{Ph\cdot NO_2}_{PhH}K$ in their calculation, since the value of 4·0 was previously used. Partial rate factors (F_o, F_m, and F_p) obtained by combination of these relative rates with the ratios of the isomeric biaryls formed in the phenylation of the compounds PhX must also be corrected. The new values of these quantities are given in Table 3.

TABLE 3. *Relative rates and partial rate factors for phenylation of benzene derivatives* (80°).

Compound (ArH)	F_o	F_m	F_p	${}^{ArH}_{PhH}K$
$Ph\cdot NO_2$ [1, 4]	5·5	0·86	4·9	2·94
PhF [8]	1·7	0·95	0·86	1·03
PhCl [1, 9, 10]	1·6	1·0	1·2	1·06
PhBr [8]	1·9	1·3	1·3	1·29
PhI [8]	2·0	1·3	1·3	1·32
PhMe [11]	2·5	0·71	1·0	1·23
PhEt [11]	1·4	0·76	1·0	0·90
$PhPr^i$ [11]	0·60	0·81	1·0	0·64
$PhBu^t$ [12]	0·46	0·94	1·0	0·64
Ph_2 [13]	2·1	1·0	2·5	2·94
$p\text{-}C_6H_4Cl_2$ [9]	—	—	—	1·98
$1,3,5\text{-}C_6H_3Cl_3$ [9]	—	—	—	3·68
$p\text{-}C_6H_4Bu^t_2$ [13]	—	—	—	0·47

The corrections in all the above cases take the form of a small reduction in the absolute values of these quantities, although their order of magnitude and relationship to one another, and hence the conclusions drawn from them in previous papers in this series, remain unaltered. Moreover, the alterations are not sufficiently great to affect the validity of qualitative arguments [2,14] based on comparisons of partial rate factors for phenylation with those for arylation with substituted aryl radicals.

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[8] Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412.
[9] Augood, Hey, and Williams, *J.*, 1953, 44.
[10] Chang, Hey, and Williams, *J.*, 1958, 2600.
[11] Hey, Pengilly, and Williams, *J.*, 1956, 1463.
[12] Cadogan, Hey, and Williams, *J.*, 1954, 3352.
[13] Cadogan, Hey, and Williams, *J.*, 1954, 794.
[14] Hambling, Hey, and Williams, *J.*, 1960, 3782.

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113. *Physical Properties and Chemical Constitution. Part XXXII.* Thiophen Compounds.*

By G. H. Jeffery, R. Parker, and A. I. Vogel.

Pure samples of thiophen, 2-n-alkylthiophens (methyl to n-heptyl), n-alkyl 2-thenoates (methyl to n-heptyl), n-alkyl 2-thienyl ketones (methyl to n-hexyl), and a number of miscellaneous sulphur compounds have been prepared and their physical properties (refractive indices at 20° and densities and surface tensions over a range of temperature) determined: the ultraviolet and infrared spectra were measured in detail for a number of representative compounds. The parachors, molecular refractions, and molecular refraction coefficients for the 2-thienyl group have been evaluated from the new experimental data.

The present investigation was undertaken to secure trustworthy data on the physical properties of pure n-alkylthiophens, n-alkyl 2-thenoates, n-alkyl 2-thienyl ketones, and 2-halogenothiophens, and to evaluate the refractions, molecular refraction coefficients, and parachors of the thienyl group and their dependence upon different substituents in the 2-position. The constants for the thienyl group in the various series were calculated in the usual manner (cf. Part XXVIII [1]) and are summarised in Table 1.

Table 1. *Mean constants for the 2-thienyl group.*

Compounds	P	$[R]_C$	$[R]_D$	$[R]_F$	$[R]_{G'}$	Mn_D^{20}
Thiophen	169·1	22·56	22·69	23·27	23·58	124·4
2-n-Alkylthiophens	167·5	22·86	23·00	23·56	24·01	124·5
s†	0·35	0·02	0·02	0·11	0·03	0·27
n-Alkyl 2-thenoates	173·8	23·83	24·08	24·78	25·37	127·6
s	0·05	0·02	0·01	0·02	0·02	0·28
n-Alkyl 2-thienyl ketones	172·1	23·88	23·99	24·83	25·62	129·8
s	0·21	0·01	0·01	0·02	0·01	0·28
2-Chlorothiophen	165·6	22·62	22·80	23·37	23·67	126·7
2-Bromothiophen	165·8	22·53	22·71	23·20	23·51	134·1
2-Iodothiophen	167·1	22·42	22·63	23·15	23·27	144·7
2-Cyanothiophen	176·5	23·80	24·05	24·70	25·27	128·0

† s = Standard deviation.

The variation of the constants for the 2-thienyl group compared with the values deduced from thiophen is very marked, and it is hoped to discuss this in a future communication.

The mean values for the CH_2 increments in the three series of compounds are in good agreement with those previously found (cf. Part XXIII [2]).

Experimental

Physical Measurements.—Details of methods are given in Part XXVIII.[1] Unless otherwise stated, b. p.s are corrected. The compounds were refractionated immediately before the measurements were made; they were examined for impurities by vapour-phase chromatography (a Griffin and George apparatus, Mark II, was used), and by ultraviolet and infrared spectroscopy, but none was found.

Materials.—Thiophen. Commercially pure thiophen (1 l.) (Hopkin & Williams) was dried ($MgSO_4$) and slowly distilled in a Towers distillation unit filled with 1/16″ Dixon gauze stainless-steel rings and fitted with a variable take-off head; the reflux ratio was 25 : 1. A middle fraction of constant b. p. and n_D^{20} (1·5287) was separated and refractionated in the same apparatus.

n-Alkyl thienyl ketones. The 2-methyl to 2-n-butyl compounds were prepared from pure

* Part XXXI, *J.*, 1960, 4728.

[1] Part XXVIII, *J.*, 1960, 4454.

[2] Part XXIII, *J.*, 1948, 1842.

TABLE 2.

No.	Compound	B. p./mm.	d_4^{20}	d_4^{40}	d_4^{60}	d_4^{85}	γ^{20}	γ^{40}	γ^{60}	γ^{85}	P	Note
798	Thiophen	84°	1·0644	1·0405	1·0162	—	31·30	28·75	26·01	—	187·0	*a*
				Alkylthiophens								
799	2-Methyl	112	1·0193	0·9978	0·9763	0·9460	30·95	28·17	25·51	22·67	226·8	*b*
800	2-Ethyl	134	0·9921	0·9726	0·9534	0·9277	30·05	27·71	25·37	23·45	264·8	*c*
801	2-n-Propyl	55·5°/20	0·9698	0·9531	0·9337	0·9079	29·67	27·65	25·62	23·12	303·7	
802	2-n-Butyl	64·5/7	0·9537	0·9389	0·9209	0·9886	29·74	27·94	26·14	23·89	343·3	
803	2-n-Pentyl	74·5/8	0·9430	0·9264	0·9097	0·8881	30·11	28·05	26·44	23·83	383·2	
804	2-n-Hexyl	76/0·9	0·9335	0·9182	0·9032	0·8820	29·95	28·25	26·57	23·89	422·6	*f*
805	2-n-Heptyl	81·5/0·3	0·9269	0·9118	0·8966	0·8774	30·40	28·53	26·68	24·35	462·1	
806	3-Methyl	115·5	1·0217	1·0007	0·9790	0·9552	32·37	29·88	27·44	24·51	229·0	*g*
807	2,5-Dimethyl	135	0·9848	0·9648	0·9441	0·9171	30·57	28·11	25·24	23·45	268·1	
				Alkyl 2-thenoates								
808	Methyl	75·5/7	1·2289	1·2081	1·1873	1·1575	39·66	36·58	34·16	31·78	290·6	*i*
809	Ethyl	97/14	1·1625	1·1423	1·1224	1·0974	36·77	34·93	32·21	29·31	331·4	*i*
810	n-Propyl	88·5/9	1·1215	1·1013	1·0851	1·0618	34·20	31·23	30·02	28·30	368·2	*i*
811	n-Butyl	83/1	1·0872	1·0691	1·0512	1·0282	33·11	30·91	28·73	—	407·4	*i*
812	n-Pentyl	101·5/4	1·0700	1·0546	1·0375	1·0173	32·60	30·71	28·39	27·01	445·6	*i*
813	n-Hexyl	125·5/6	1·0505	1·0286	1·0079	0·9824	32·58	30·03	27·63	—	483·8	
814	n-Heptyl	133/3	1·0315	1·0153	0·9990	0·9810	31·71	30·08	28·18	26·11	522·0	
				Alkyl 2-thienyl ketones								
815	Methyl	107/23	1·1707	1·1517	1·1325	1·1098	42·72	38·85	36·63	32·93	273·9	*j*
816	Ethyl	108/18	1·1312	1·1130	1·0948	1·0733	39·96	36·69	34·44	31·99	310·6	*k*
817	n-Propyl	108/11	1·0955	1·0761	1·0593	1·0383	37·29	34·69	33·04	32·00	348·9	*k*
818	Isopropyl	79/1	1·0880	1·0719	1·0530	1·0309	37·01	35·29	33·41	31·13	351·5	*k*
819	n-Butyl	131·5/20	1·0682	1·0490	1·0311	1·0108	35·66	33·90	32·17	30·03	387·0	*k*
820	n-Pentyl	107/3	1·0458	1·0292	1·0130	0·9945	34·70	33·24	31·36	29·09	424·9	*k*
821	n-Hexyl	110·5/4	1·0313	1·0151	1·0094	0·9891	34·17	32·84	31·24	28·81	463·0	
				Halogenothiophens								
822	2-Chloro-	121	1·2862	1·2618	1·2347	1·2064	34·03	31·72	29·37	27·01	223·0	*l*
823	2-Bromo-	152	1·7071	1·6781	1·6632	1·6121	37·37	35·36	33·24	30·49	236·2	*m*
824	2-Iodo-	60/4	2·0645	2·0334	2·0006	1·9600	42·59	40·46	38·36	35·48	260·0	*n*
825	2,5-Dichloro-	65·5/23	1·4422	1·4154	1·3886	1·3541	37·77	35·75	34·28	29·89	263·2	*o*
826	2,5-Dibromo-	68/2	2·1439	2·1110	2·0741	2·0246	43·50	42·23	39·21	36·46	290·9	
				2-Thienylcarbinols								
827	Methyl	82·5/4	1·1495	1·1301	1·1140	1·0907	40·40	37·74	33·81	32·43	280·9	
828	Ethyl	75/1·5	1·1079	1·0915	1·0752	1·0503	36·75	34·95	32·91	30·70	317·0	
829	n-Propyl	97·5/5	1·0764	1·0599	1·0429	1·0216	36·23	34·21	31·93	29·34	356·2	
				Miscellaneous sulphur compounds								
830	2-Benzylthiophen	95·5/1	1·0999	1·0845	1·0690	—	42·23	39·86		—	403·9	
831	2-Cyanothiophen	73/10	1·1778	1·1586	1·1380	1·1129	46·42	43·74	41·02	37·55	242·2	
832	2-Methoxythiophen	51/15	1·1335	1·1120	1·0919	1·0689	36·52	34·38	31·46	28·91	248·0	*r*
833	2-Ethoxythiophen	62/11	1·0805	1·0603	1·0398	1·0147	33·82	31·54	29·69	27·10	287·1	*r*
834	Thiophen-2-aldehyde	73·5/11	1·2264	1·2080	1·1888	1·1657	49·25	46·23	44·01	—	242·3	*s*
835	Tetrahydrothiophen	120	0·9989	0·9801	0·9615	0·9398	35·68	33·21	30·86	26·98	216·4	*t*
836	Tetrahydrothiophen oxide	90/0·8	1·1725	1·1569	1·1392	1·1177	49·77	46·61	43·84	41·54	235·7	
837	Tetrahydrothiophen dioxide	117/1	—	1·2549	1·2358	1·2161	—	49·46	43·11	35·65	252·6	*u*
838	Thiacyclohexane	93/82	0·9861	0·9681	0·9488	0·9255	36·06	33·74	31·17	—	254·4	*v*
839	Thiacyclobutane	94	1·0228	1·0017	0·9817	0·9566	34·60	—	—	—	177·0	*w*
840	1,4-Thioxan	147	1·1171	1·0990	1·0812	1·0587	42·39	40·54	37·49	34·23	238·4	*x*

For footnotes see under Table 3.

XUM

dry thiophen and the redistilled acid anhydride in the presence of orthophosphoric acid as catalyst.[3] n-Pentyl, n-hexyl, and isopropyl 2-thienyl ketone were obtained from pure dry thiophen and the appropriate redistilled acid chloride in the presence of orthophosphoric acid as catalyst.[4]

TABLE 3.

No.	n_C^{20}	n_D^{20}	n_F^{20}	n_G^{20}	$[R]_C$	$[R]_D$	$[R]_F$	$[R]_G$	Mn_D^{20}	Note
798	1·52385	1·52866	1·54109	1·55196	24·23	24·37	24·96	25·28	128·31	*a*
				Alkylthiophens						
799	1·51553	1·52013	1·53196	1·53841	29·07	29·29	29·85	30·15	149·26	*b*
800	1·50805	1·51223	1·52335	1·53240	33·71	33·94	34·56	35·06	169·61	*c*
801	1·50168	1·50575	1·51606	1·52487	38·38	38·65	39·31	39·85	190·01	*d*
802	1·49635	1·50021	1·51041	1·51915	43·03	43·32	44·06	44·66	210·43	*e*
803	1·49484	1·49851	1·50798	1·51638	47·67	47·97	48·74	49·42	231·10	
804	1·49198	1·49556	1·50466	1·51302	52·29	52·63	53·43	54·18	251·80	
805	1·49035	1·49384	1·50265	1·51097	56·90	57·26	58·11	58·93	270·24	
806	1·51581	1·52035	1·53201	1·54213	29·01	29·23	29·77	30·24	149·24	*g*
807	1·50789	1·51240	1·52377	1·53279	33·97	34·22	34·86	35·36	169·66	*h*
				Alkyl 2-thenoates						
808	1·53671	1·54229	1·55711	1·56872	36·11	36·42	37·25	37·89	219·31	*i*
809	1·52001	1·52510	1·53859	1·55096	40·85	41·19	42·07	42·87	238·21	*i*
810	1·51245	1·51724	1·52990	1·53959	45·57	45·93	46·87	47·58	258·20	*i*
811	1·50436	1·50881	1·52056	1·53004	50·21	50·58	51·58	52·34	278·01	*i*
812	1·50330	1·50772	1·51896	1·52834	54·82	55·22	57·10	56·25	289·96	*i*
813	1·49980	1·50395	1·51488	1·52403	59·43	59·85	60·93	61·84	319·21	
814	1·49587	1·49983	1·51022	1·51914	64·08	64·51	65·61	66·61	338·89	
				Alkyl 2-thienyl ketones						
815	1·56012	1·56681	1·58506	1·59719	34·85	35·19	36·03	36·72	197·68	*j*
816	1·54829	1·55436	1·57082	1·58629	39·41	39·75	40·64	41·62	217·93	*k*
817	1·53788	1·54356	1·55884	1·57317	44·05	44·41	45·43	46·46	238·05	*k*
818	1·53570	1·54134	1·55672	1·57109	44·18	44·56	45·61	46·58	237·70	*k*
819	1·53016	1·53545	1·54981	—	48·68	49·09	50·14	—	258·33	*k*
820	1·52943	1·52953	1·54302	1·55561	53·33	53·77	54·88	56·03	278·79	*k*
821	1·52135	1·52617	1·53929	1·54869	57·97	58·44	59·60	60·83	299·58	
				Halogenothiophens						
822	1·54386	1·54888	1·56172	1·57145	29·10	29·32	29·95	30·31	183·66	*l*
823	1·58142	1·58705	1·60163	1·61181	31·84	32·10	32·74	33·19	258·75	*m*
824	1·64550	1·65290	1·67225	1·68149	36·89	37·24	38·11	38·55	347·16	
825	1·55778	1·56286	1·57657	1·58861	34·20	34·46	35·15	35·74	239·20	*o*
826	1·62222	1·62863	1·64547	1·66049	39·76	40·08	40·94	41·69	394·05	*p*
				2-Thienylcarbinols						
827	1·54327	1·54803	1·56032	1·56976	35·16	35·42	36·08	36·57	198·42	*q*
828	1·53417	1·53856	1·55017	1·55953	39·89	40·22	40·92	41·50	218·80	*q*
829	1·52764	1·53228	1·54439	1·55390	44·70	45·00	45·86	46·42	239·41	*q*
				Miscellaneous sulphur compounds						
830	1·58638	1·59125	1·60722	1·62030	53·20	53·55	54·72	55·67	277·31	
831	1·55870	1·56486	1·58114	1·59593	29·89	30·17	30·87	31·51	170·76	
832	1·52273	1·52738	1·53932	1·54882	30·75	31·00	31·56	32·03	174·47	
833	1·50988	1·51418	1·52518	1·53424	35·47	35·73	36·36	36·88	194·10	*t*
834	1·58278	1·59085	1·61313	1·63481	30·55	30·89	31·83	32·73	178·41	*s*
835	1·50108	1·50430	1·51243	1·52193	26·01	26·16	26·51	26·94	132·61	*t*
836	1·51896	1·52221	1·53028	1·53668	26·96,	27·10	27·49	27·73	158·56	
837	1·48302	1·48538	1·49117	1·49584	27·00	27·11	27·39	27·61	178·50	*u*
838	1·50354	1·50698	1·51484	1·52272	30·66	30·83	31·24	31·64	153·97	*v*
839	1·50530	1·50887	1·51794	1·52613	21·51	21·64	21·96	22·25	111·86	*w*
840	1·50432	1·50748	1·51558	1·52221	27·62	27·77	28·14	28·44	157·02	*x*

n-Alkylthiophens. 2-Methylthiophen was prepared from sodium lævulate and phosphorus trisulphide.[5] 2-Ethyl- and 2-n-propyl-thiophen were obtained from 2-acetyl- and 2-propionyl-thiophen by Huang-Minlon's modification of the Wolff–Kishner reduction.[6] n-Butyl-,

[3] See Kosak and Hartough, *Org. Synth.*, Coll. Vol. III, p. 14.
[4] Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 3093.
[5] Hartough, "Thiophene and its Derivatives," p. 495, Interscience Publ. Inc., New York, 1952.
[6] Buu-Hoï, *J. Org. Chem.*, 1950, **15**, 957; King and Nord, *ibid.*, 1949, **14**, 638.

XUM

n-pentyl-, n-hexyl-, and n-heptyl-thiophen were prepared by interaction of pure thiophen and the appropriate alkyl bromide in liquid ammonia solution in the presence of sodamide (cf. preparation of n-alkylpyridines, Part XXVIII [1]); the products were isolated by fractionation under reduced pressure. 3-Methylthiophen was obtained from redistilled sodium methyl succinate and phosphorus pentasulphide in the presence of a mineral oil; [7] 2,5-dimethylthiophen was prepared from acetonylacetone and phosphorus trisulphide.[8]

n-Alkyl 2-thenoates. 2-Thenoic acid was prepared by oxidation of pure 2-acetylthiophen with potassium hypochlorite by an adaptation of the method for conversion of 2-acetylnaphthalene into naphthoic acid,[9] and was recrystallised from hot water; it had m. p. 130°. The acid was converted into 2-thenoyl chloride with excess of pure thionyl chloride; the excess of the latter was removed by distillation on a water-bath, and the residue treated with the calculated quantity of the pure alcohol (methyl to n-butyl, n-hexyl, and n-heptyl thenoate). n-Pentyl thenoate was obtained by refluxing a mixture of the acid, pure n-pentyl alcohol, and benzene in the presence of Zeo-Karb 225H and was isolated in the usual manner.[10]

2-Chlorothiophen. This was prepared from pure thiophen (1 mol.) and redistilled sulphuryl chloride (1 mol.) and isolated by fractionation.[11]

2-Bromothiophen. This was obtained by treatment of thiophen (1 mol.) in carbon tetrachloride with bromine (0·95 mol.) in carbon tetrachloride at 0—10° and was isolated by fractionation.[12]

2-Iodothiophen. Interaction of thiophen with iodine in the presence of mercuric oxide [13] yielded, after fractional distillation at low pressure, the pure colourless 2-iodothiophen.

2,5-Dichlorothiophen. This was prepared from thiophen and sulphuryl chloride in the presence of iodine as catalyst.[12]

2,5-Dibromothiophen. A commercial sample (Fluka) was carefully fractionated under reduced pressure through a 4″ column filled with Fenske helices.

Thiophen-2-aldehyde. Interaction of thiophen with *N*-methylformanilide and phosphorus oxychloride [14] gave a light red oil, b. p. 66—67°/4 mm. This was steam-distilled in the presence of aqueous sodium hydrogen carbonate, a Dean and Stark apparatus being used as receiver for the aldehyde–water mixture: the colourless aldehyde was isolated by ether-extraction,

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Footnotes to Table 3.

(*a*) Fawcett and Rasmussen (*J. Amer. Chem. Soc.*, 1945, **67**, 1705) give d_4^{20} 1·0644, n_D^{20} 1·5287, *P* 187·4. (*b*) Fawcett (*ibid.*, 1946, **68**, 1420) gives d_4^{20} 1·0194, n_D^{20} 1·5203; Haines (*J. Phys. Chem.*, 1956, **60**, 551) gives d_4^{20} 1·01965, n_D^{20} 1·5203. (*c*) von Auwers and Kohlhaas (*J. prakt. Chem.*, 1924, **108**, 322) give $d_4^{21\cdot2}$ 0·9908. (*d*) Scheibler and Schmidt (*Ber.*, 1921, **54**, 149) give n_D^{20} 1·5048. (*e*) Pines *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 5173) give n_D^{20} 1·5004. (*f*) Campaigne and Diedrich (*ibid.*, 1948, **70**, 391) give d_4^{20} 0·946, n_D^{20} 1·4970. (*g*) Fawcett (*loc. cit.*) gives d_4^{20} 1·0216, n_D^{20} 1·5204; Haines (*loc. cit.*) gives d_4^{20} 1·02183, n_D^{20} 1·5204, *P* 228·2. (*h*) Hartough (*J. Amer. Chem. Soc.*, 1951, **73**, 4035) gives n_D^{20} 1·5128. (*i*) Weinstein (*ibid.*, 1955, **77**, 6709) gives methyl, d_4^{20} 1·2290, n_D^{20} 1·5420; ethyl, d_4^{20} 1·1620, n_D^{20} 1·5248; n-propyl, d_4^{20} 1·1123, n_D^{20} 1·5170; n-butyl, d_4^{20} 1·0859, n_D^{20} 1·5122; n-pentyl, d_4^{20} 1·0573, n_D^{20} 1·5071. (*j*) Johnson (*ibid.*, 1947, **69**, 150) gives d_4^{20} 1·1709, n_D^{20} 1·5667, γ^{30} 44·5 (*k*) Spurlock (*ibid.*, 1953, **75**, 1115) gives ethyl, d^{20} 1·1390, n_D^{20} 1·5538; n-propyl, d^{20} 1·0941, n_D^{20} 1·5434; isopropyl, d^{20} 1·0894, n_D^{20} 1·5405; n-butyl, d^{20} 1·0664, n_D^{20} 1·5357; n-pentyl, d^{20} 1·0473, n_D^{20} 1·5301. (*l*) Coonradt, Hartough, and Johnson (*ibid.*, 1948, **70**, 2564) give d_4^{20} 1·2863, n_D^{20} 1·5487. (*m*) Keswani and Freiser (*ibid.*, 1949, **71**, 218) give d_4^{20} 1·6929, n_D^{20} 1·5815. (*n*) Keswani and Freiser (*loc. cit.*) give d_4^{20} 2·0493. (*o*) Coonradt *et al.* (*loc. cit.*) give d_4^{20} 1·4422, n_D^{20} 1·5626. (*p*) Steinkopf (*Annalen*, 1937, **532**, 250) gives n_D^{20} 1·6275. (*q*) Van Zyl *et al.*[17] give ethanol, n_D^{25} 1·5430; propanol, n_D^{25} 1·5318; butanol, n_D^{25} 1·5220. (*r*) Sicé [16] gives methoxy, d_4^{25} 1·1200, n_D^{25} 1·5261; ethoxy, d_4^{27} 1·075, n_D^{27} 1·5116. (*s*) Keswani and Freiser (*loc. cit.*) give d_4^{20} 1·2143, n_D^{30} 1·5838. (*t*) Haines (*loc. cit.*) gives d_4^{20} 0·9986, n_D^{20} 1·5048. (*u*) Solid, m. p. 24·8°; values at 20° (extrapolated), n_D^{30} 1·48188; n_D^{35} 1·48013. (*v*) Haines (*loc. cit.*) gives d_4^{20} 0·9856, n_D^{20} 1·50682. (*w*) Haines (*loc. cit.*) gives d_4^{20} 1·0200, n_D^{20} 1·5102. (*x*) Clark (*J.*, 1912, **101**, 1788) gives d_4^{20} 1·1178, n_C^{20} 1·50429, n_G^{20} 1·52223.

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[7] Feldkamp and Tullar, *Org. Synth.*, 1954, **34**, 73.

[8] Buu-Hoï and Nguyen-Hoan, *Rec. Trav. chim.*, 1948, **67**, 309; cf. ref. 5.

[9] (*a*) Newman and Holmes, *Org. Synth.*, Coll. Vol. II, p. 428, John Wiley & Sons, New York, 1943; (*b*) Hartough and Conley, *J. Amer. Chem. Soc.*, 1947, **69**, 3096.

[10] Sussman, *Ind. Eng. Chem.*, 1946, **38**, 1228; Vogel, " Practical Organic Chemistry," 3rd edn., p. 387, Longmans, Green & Co., London.

[11] Campaigne and Le Suer, *J. Amer. Chem. Soc.*, 1948, **70**, 415.

[12] Cf. Hartough, ref. 5, p. 498.

[13] Minnis, ref. 9*a*, p. 44.

[14] King and Nord, *J. Org. Chem.*, 1948, **13**, 635; Weston and Michaels, *J. Amer. Chem. Soc.*, 1950, **72**, 1422.

XUM

and the ethereal extract dried, and, after removal of the ether, distilled in nitrogen under reduced pressure through a 6″ Fenske column.

2-Cyanothiophen. Pure thiophen-2-aldehyde was converted by hydroxylammonium chloride into the oxime, m. p. 128°, and the latter warmed gently with a mixture of acetic anhydride and anhydrous sodium acetate.[15] The nitrile, isolated as usual, was distilled first at normal pressure (b. p. 192—193°) and then under reduced pressure.

2-Methoxythiophen. This was prepared by refluxing 2-iodothiophen and methanolic sodium methoxide for 30 hr. in the presence of powdered cupric oxide; it boiled[16] constantly at 75—76°/50 mm.

2-Ethoxythiophen. This was prepared similarly to methoxythiophen.

2-Thienyl-carbinols. 2-Thienyl-ethanol, -propan-1-ol, and -butan-1-ol were prepared by the interaction of 2-thienylmagnesium bromide and the appropriate aldehyde.[17] All were isolated by fractionation at 2—3 mm.

2-Benzylthiophen. Anhydrous zinc chloride (50 g.) was added during 1 hr. to a boiling mixture of thiophen (50 g.) and benzyl alcohol (50 g.); the 2-benzylthiophen, b. p. 115—116°/10 mm. (24 g.), was isolated by steam-distillation and ether-extraction.[18]

Tetrahydrothiophen. This was obtained from redistilled 1,4-dichlorobutane and sodium sulphide in dimethylformamide.[19]

Tetrahydrothiophen oxide and dioxide. Commercial samples (Robinson Bros., West Bromwich) were dried and fractionated under reduced pressure through a 6″ Fenske column.

Thiacyclohexane. This was prepared by adding 1,5-dibromopentane to a boiling sodium sulphide solution, and refluxing the whole for 4 hr., with final steam-distillation.[20]

Thiacyclobutane. This was obtained from alcoholic sodium sulphide and trimethylene dibromide.[21]

1,4-Thioxan. A commercial sample (Robinson Bros., West Bromwich), dried and redistilled, had b. p. 146·0°/759 mm.

Tables 2 and 3 summarise the physical properties of all the pure compounds investigated; the numbering of compounds in Clarendon type follows from Part XXXI.[22] Table 2 contains the b. p. (at 760 mm., unless otherwise stated), rounded values of the density and surface tension at various temperatures, and the mean parachor, whilst Table 3 gives the refractive indices, molar refractivities, and the molar refraction coefficients.

Ultraviolet Spectra.—Measurements were made in matched 1 cm. silica cells on a Unicam spectrophotometer S.P. 500. n-Hexane " free from aromatic hydrocarbons " was purified by percolation through a 40″ column of silica gel (14—20 mesh). Burroughs's absolute ethyl alcohol was used directly. Solutions were prepared by dissolving 10—20 mg. of the sample, accurately weighed, in 10·0 ml. of the purified solvent: 1·00 ml. of this solution was then diluted to 10 or 25 ml. in a graduated flask.

TABLE 4. *Ultraviolet absorption data.*

2-n-Alkylthiophens (in n-hexane)

Compound	10^6C	$\lambda_{max.}$	$E_{max.}$
(Thiophen)	109	231	8000
2-Ethyl ...	118	234	8000
2-n-Pentyl	118	234	8000
2-n-Hexyl	57	234	8000
3-Methyl ...	102	235	6050

2-n-Alkyl thenoates (in n-hexane)

Compound	10^6C	$\lambda_{max.}$	$E_{max.}$	$\lambda_{max.}$	$E_{max.}$	$\lambda_{max.}$	$E_{max.}$
Ethyl	59	244	15,100	250	15,100	262	12,150
n-Propyl ...	91	244	15,100	250	15,100	262	12,150
n-Heptyl ...	99	245	15,100	250	15,150	262	12,150

Halogenothiophens (in alcohol)

Compound	10^6C	$\lambda_{max.}$	$E_{max.}$
2-Chloro-	80	236	7900
2-Bromo-	82	236	8350
2,5-Dichloro-	77	252	10,050
2,5-Dibromo-	100	252	10,150

Miscellaneous sulphur compounds (in alcohol)

2-Benzylthiophen ...	87	235	10,000
2-Cyanothiophen	90	242	18,900
Thiophen-2-aldehyde	85	261	14,000
Tetrahydrothiophen	83	210	1000
Thiacyclohexane	82	210	1000

[15] Putoknin and Egorova, *J. Gen. Chem.* (*U.S.S.R.*), 1948, **18**, 1866; *Chem. Abs.*, 1949, **43**, 3816.
[16] Sicé, *J. Amer. Chem. Soc.*, 1953, **75**, 3697.
[17] Van Zyl, Langenberg, Tan, and Schut, *J. Amer. Chem. Soc.*, 1956, **78**, 1955.
[18] Steinkopf, *Annalen*, 1939, **541**, 257.
[19] Lawson, Easlay, and Wagner, *Org. Synth.*, 1956, **36**, 89.
[20] Haines, *J. Phys. Chem.*, 1956, **60**, 549.
[21] Bennett and Hock, *J.*, 1927, 2496.
[22] Part XXXI, *J.*, 1960, 4728.

Some typical results are collected in Table 4. Concentrations C are expressed in moles per l.; $\lambda_{max.}$ is given in mμ. Data for a few thiophen compounds in iso-octane have been published [23] and are in excellent agreement with ours.

Infrared Spectra.—The infrared absorption spectra (capillary film) were kindly measured by Mr. R. F. Branch, B.Sc., of the Ministry of Supply, Woolwich, using a Perkin–Elmer double-beam instrument with a rock-salt prism. Typical spectra, including those for which the ultraviolet spectra are recorded above, are contained in ref. 24. The infrared spectra published for some alkyl- and halogeno-thiophens [25] agreed well with our own.

The authors thank Imperial Chemical Industries Limited for a grant.

DEPARTMENT OF CHEMISTRY, WOOLWICH POLYTECHNIC,
LONDON, S.E.18. [*Received, July 22nd,* 1960.]

[23] Ref. 5, p. 101.
[24] R. S. Parker, Ph.D. Thesis, University of London, 1958.
[25] Ref. 5, pp. 109—127.

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114. *Competition between Aniline and Phenol for a Triphenylmethyl Cation.*

By GABRIEL CHUCHANI.

It has been shown previously that, on tritylation of *o*-aminophenol, the triphenylmethyl group enters the *para*-position with respect to the hydroxyl group. Results now obtained in experiments in which phenol and aniline compete for several trityl reagents reverse the order: *i.e.*, $NH_2 > OH$. The case of *o*-aminophenol is therefore anomalous and may be due to the juxtaposition of the two groups.

TRITYLATION of *o*-aminophenol [1,2] suggested that the directive power of hydroxyl exceeds that of amino, and similar results have been obtained in the present work by using triphenylmethanol or its perchlorate as tritylating agent. In extension of this work, aniline and phenol (10 mol. of each) were allowed to compete [3] for several trityl reagents (1 mol.) at different temperatures and for a long time. The results given in the Table are of only qualitative significance, but the average yields obtained clearly show that in every case

Competition between aniline and phenol for triphenylmethyl carbonium ion [a]

Reagent	Temp.	Average yield (%) Posn. of CPh_3 4 ($NH_2 = 1$)	4 ($OH = 1$)	Reagent	Temp.	Average yield (%) Posn. of CPh_3 4 ($NH_2 = 1$)	4 ($OH = 1$)
Triphenylmethanol [b]	Reflux	82	2	Chlorotriphenylmethane	90—100°	85	—
					140—145°	83	—
Triphenylmethanol [c]	Reflux	75	0·5		Reflux	84	5
Triphenylmethanol [d]	140—145°	61	12	Triphenylmethyl perchlorate	100—105°	78	—
	Reflux	59	22		Reflux	84	—

[a] Average isolated yields were taken from three runs; products were identified by mixed m. p. [b] AcOH–HCl. [c] AcOH–H_2SO_4. [d] Without solvent and catalyst.

NH_2 predominates over OH in control of orientation in strong acid media. This supports our view [2] that the amino-group is un-ionized at the moment of condensation: if the NH_3^+ group were present we would expect OH to exceed NH_2 in directive power.

The anomalous results obtained earlier [1,2] with *o*-aminophenol may be due to the intramolecular changes illustrated in (I)—(IV). If such a chelation occurred intermolecularly in mixtures of aniline and phenol, we should expect to obtain species such as

[1] Chuchani, *J.*, 1959, 1753.
[2] Chuchani, *J.*, 1960, 325.
[3] See (*a*) Ingold and Shaw, *J.*, 1927, 2918; (*b*) Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, pp. 221—305.

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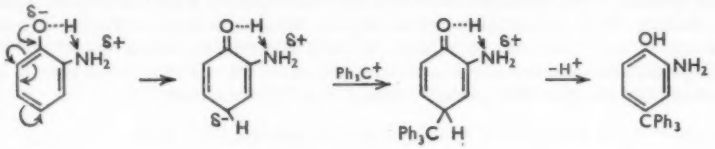
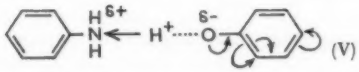
(V). In that case we should have an $:O^-$ group which would be stronger in orientational control than the NH_3^+ group, contrary to the experimental results. The present finding is in agreement with that of inorganic electrophilic substitution in aromatic compounds.



(I) (II) (III) (IV)



(V)

At the same time, our evidence presents further support for the generalization [3b] N > O in orientational control, indicating a decrease in the directing power due to an increase in unshared electrons as the group number increases.[3b,4,5]

Experimental

Triphenylmethyl perchlorate was prepared as described by Gomberg and Cone.[6]

p-Triphenylmethylphenol was prepared from triphenylmethanol and phenol as described by Boyd and Hardy,[7] and also by heating triphenylmethyl perchlorate (0·01 mole) with phenol (0·015 mole) at 80—90° for 5 hr., the solid mass being crystallized from glacial acetic acid; it had m. p. and mixed m. p.[8,9] 284—286° (yield 86%).

p-*Triphenylmethylaniline.*—(*a*) Triphenylmethanol (0·01 mole) and aniline (0·015 mole) were gently refluxed under nitrogen for 17 hr., and the product was crystallized from toluene; it had m. p. 256—258° (yield 60%) alone or mixed with the product from tritylation of aniline.[8,10] (*b*) Triphenylmethyl perchlorate (0·01 mole) was heated with aniline (0·015 mole) at 140—145° for 6 hr., then treated with 20% sodium hydrogen carbonate solution (10 ml.) and dissolved in glacial acetic acid. The mixture was diluted with water (100 ml.), and the solid filtered off and crystallized from toluene; it had m. p. 256—258° (yield 63%) undepressed on admixture with an authentic sample.[8,10]

2-*Amino*-4-*triphenylmethylphenol.*—(*a*) Triphenylmethanol (0·01 mole) and *o*-aminophenol (0·015 mole) were heated together at 130—135° for 12 hr. The product was heated with glacial acetic acid, diluted with water (200 ml.), and treated with 50% sodium hydroxide solution; the precipitate, crystallized from toluene, had m. p. 287—290° (yield 46%) alone and mixed with a previous specimen.[1,2] (*b*) Triphenylmethyl perchlorate (0·01 mole) was heated with *o*-aminophenol (0·015 mole) at 130—140° for 6 hr. The solid was filtered off and crystallized from toluene; m. p. and mixed m. p.[1,2] 287—289 (yield 51%).

Competition between Aniline and Phenol.—(i) *For triphenylmethanol with hydrochloric acid as catalyst.* A mixture of triphenylmethanol (0·01 mole), aniline (0·1 mole), phenol (0·1 mole), and glacial acetic acid (150 ml.) was heated until homogeneous, then refluxed for 1 week after addition of concentrated hydrochloric acid (4 ml.). After dilution with water (400 ml.), the mixture was treated with 50% sodium hydroxide solution until no more precipitate was formed. The resulting solid was refluxed with ethanolic potassium hydroxide (10 g. in 50 ml.), and the mixture diluted with an equal volume of water and filtered. The solid was crystallized from toluene–ethanol (product A), and the filtrate was acidified with concentrated hydrochloric acid, giving a solid (B). The crystals (A), m. p. 256—258°, were proved (mixed m. p.) to be *p*-triphenylmethylaniline,[8,9] and the solid (B), crystallized from glacial acetic acid, had m. p. alone

[4] Ingold and Ingold, *J.*, 1926, 1310.
[5] Holmes and Ingold, *J.*, 1926, 1328.
[6] Gomberg and Cone, *Annalen*, 1909, **370**, 193.
[7] Boyd and Hardy, *J.*, 1928, 630.
[8] MacKenzie and Chuchani, *J. Org. Chem.*, 1955, **20**, 338.
[9] Baeyer and Villiger, *Ber.*, 1902, **35**, 1189.
[10] Ullmann and Munzhuber, *Ber.*, 1902, **35**, 2878.

XUM

or mixed with *p*-triphenylmethylphenol [8,9] 284—286°. Yields from triplicate runs were: *p*-tritylaniline 78, 93, 75%; *p*-tritylphenol 3, 2, 0·6%, respectively.

(ii) *For triphenylmethanol with sulphuric acid as catalyst.* Conditions were as in (i) except that concentrated sulphuric acid (4 ml.) replaced hydrochloric acid. Yields were: *p*-tritylaniline 81, 66, 78%; *p*-tritylphenol 0·3, 0·3, 0·9%, respectively.

(iii) *For chlorotriphenylmethane.* (*a*) Phenol (0·1 mole) and aniline (0·1 mole) were heated to about 60° until homogeneous, and chlorotriphenylmethane (0·01 mole) was added. The mixture was heated at 90—100° for 24 hr. under nitrogen, then with glacial acetic acid. Working up as in (i) gave: *p*-tritylaniline 78, 93, 84%; and unidentified traces. (*b*) As in (*a*) but with 24 hours' heating at 140—145°. Yields were: *p*-tritylaniline 81, 81, 87%; and unidentified traces. (*c*) As in (*a*) but with 24 hours' heating under reflux. Yields were: *p*-tritylaniline 87, 78, 87%; *p*-tritylphenol 4·5, 5·3, 5·3%, respectively.

(iv) *For triphenylmethanol alone.* (*a*) Phenol (0·1 mole), aniline (0·1 mole), and triphenylmethanol (0·01 mole) were heated at 140—145° for 24 hr. under nitrogen. Working up as in (i) gave: *p*-tritylaniline 60, 57, 66%; *p*-tritylphenol 9, 18, 9%, respectively. (*b*) With 24 hours' refluxing yields were: *p*-tritylaniline 54, 60, 63%; *p*-tritylphenol 30, 18, 18%, respectively.

(v) *For triphenylmethyl perchlorate.* (*a*) Phenol (0·1 mole) and aniline (0·1 mole) were heated at about 60° until homogeneous, and triphenylmethyl perchlorate (0·01 mole) was added. The mixture was heated at 100—105° for 24 hr. Warm glacial acetic acid was added, and the solution diluted with water and treated with 20 ml. of 50% sodium hydroxide solution. The resulting solid was filtered off and separated by the procedure described in (i). The results were: *p*-tritylaniline 76, 81, 77%; and no other product. (*b*) With 24 hours' refluxing yields were: *p*-tritylaniline 82, 88, 82%; and no other product.

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115. *Cyclopentadienylnickel–Acetylene Complexes.*

By J. F. Tilney-Bassett.

Acetylenes displace the two bridging carbonyl groups in dicyclopentadienyldinickel dicarbonyl and yield complexes of general formula $(C_5H_5Ni)_2,RC{\equiv}CR'$, from which the acetylene can be recovered unchanged. Diphenylbutadiyne has been used to prepare complexes in which nickel is bonded to one of the triple bonds, and cobalt or iron to the other.

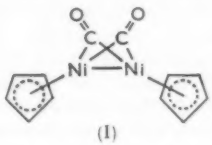
In a recent communication [1] it was suggested that dicyclopentadienyldinickel dicarbonyl (I), first prepared by Fischer and Palm,[2] is structurally in the same group as dicobalt octacarbonyl and the di-iron octacarbonyl anion. In each case it was suggested [1,3] that the bridging groups are not coplanar with the two metal atoms, but occupy two of the octahedral sites about each metal atom, whilst three others are occupied by terminal carbonyl groups, or in the case of (I) by a cyclopentadienyl group. The sixth position is unoccupied, and hence it should be readily attacked by a suitable substrate. This may provide an explanation of the catalytic activity of dicobalt octacarbonyl [4] and the di-iron octacarbonyl anion,[5] and for the ease with which both substances react with acetylenes.[6]

The above structural considerations indicated that (I) might show a similar reactivity and, as already reported in outline,[1] it does react with acetylenes giving compounds of

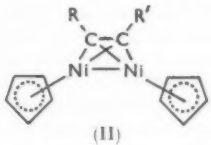
[1] Tilney-Bassett and Mills, *J. Amer. Chem. Soc.*, 1959, **81**, 4757.
[2] Fischer and Palm, *Chem. Ber.*, 1958, **91**, 1725.
[3] Mills and Robinson, *Proc. Chem. Soc.*, 1959, 156.
[4] Adkins and Kresk, *J. Amer. Chem. Soc.*, 1948, **70**, 383.
[5] Sternberg, Markby, and Wender, *J. Amer. Chem. Soc.*, 1956, **78**, 5704.
[6] Sternberg, Greenfield, Friedel, Wotiz, Markby, and Wender, *J. Amer. Chem. Soc.*, 1954, **76**, 1457; 1956, **78**, 120.

XUM

general formula $(C_5H_5Ni)_2,RC{\vdots}CR'$. The reaction is completed in refluxing toluene solution in 30—120 minutes for alkyl- or phenyl-substituted acetylenes. Diphenylacetylene gave an 88% yield of dicyclopentadienyldinickel–diphenylacetylene which was also prepared in a similar yield by refluxing dicyclopentadienylnickel, nickel carbonyl, and diphenylacetylene in benzene solution. The latter method is more convenient in this case, but leads to a less pure product from alkylacetylenes. Alkylacetylenes react cleanly with the carbonyl (I), but the yields of cyclopentadienylnickel–acetylene complexes were lower as purification was harder. In many cases cyclopentadienylnickel–acetylene complexes were not formed. Thus, acetylenedicarboxylic acid did not react with the carbonyl (I); and its dimethyl ester, although it did react, gave a small yield of tricyclopentadienyltrinickeldicarbonyl [2] rather than the expected acetylene complex. Reactions



(I)



(II)

of di-iodoacetylene and of propargyl bromide did not yield an identifiable product. Acetylene itself gave only a very low yield of dicyclopentadienyldinickel–acetylene when bubbled through a refluxing solution of the carbonyl (I) in benzene; but this is probably due to the low concentration of acetylene in boiling benzene, as Dubeck has obtained this complex in 48% yield from dicyclopentadienenickel and acetylene under pressure.[7]

All the cyclopentadienylnickel–acetylene complexes so far prepared have an intense green colour in solution. Those derived from phenyl-substituted acetylenes form black crystals and are stable in air, but those from alkyl acetylenes are slowly oxidised. All the complexes are oxidised slowly by air in solution in non-polar solvents and rapidly in polar solvents such as ethanol or acetic acid. This oxidation can be used for the recovery of the acetylene, and high yields of diphenylacetylene were obtained from the dicyclopentadienyldinickel–diphenylacetylene complex. The complexes are also oxidised by mercuric chloride, which was reduced to mercurous chloride. Recovery of acetylenes after oxidation of the cyclopentadienylnickel–acetylene complex, and also the formation of bibenzyl when the diphenylacetylene complex is reduced with sodium and alcohol in liquid ammonia, show that the diphenylacetylene residue is attached only to nickel atoms and not to carbon. These facts, together with the formal analogy of the reactions of dicyclopentadienyldinickel dicarbonyl (I) and of dicobalt octacarbonyl with acetylenes, and Dubeck's report [7] that dicyclopentadienyldinickel–acetylene complex contains no unpaired electrons, support the structure (II) proposed in our preliminary communication.[1]

Treatment of dicobalt hexacarbonyl–acetylene complexes with carbon monoxide under pressure yields dicobalt nonacarbonyl–acetylene complexes [8] which contain a maleic anhydride nucleus.[3] Treatment of compound (II; R = R′ = Ph) with carbon monoxide at 110°/70 atm. did not yield an analogous complex, but resulted in the formation of diphenylacetylene and nickel carbonyl.

The reaction of dicyclopentadienyldinickel dicarbonyl with diphenylbutadiyne yields two products, (III) and (IV), containing two and four nickel atoms per molecule, respectively, and corresponding to the reaction of, first, one and then the second triple

(III) $(C_5H_5Ni)_2(PhC{\vdots}C{\cdot}C{\vdots}CPh)$ $(C_5H_5Ni)_4(PhC{\vdots}C{\cdot}C{\vdots}CPh)$ (IV)

bond. The ease of recovery of acetylene from complexes (II) leads to the possibility that the formation of complexes of this type might be used for the protection of acetylenes.

[7] Dubeck, *J. Amer. Chem. Soc.*, 1960, **82**, 502.
[8] Sternberg, Shukys, Donn, Markby, Friedel, and Wender, *J. Amer. Chem. Soc.*, 1959, **81**, 2339.

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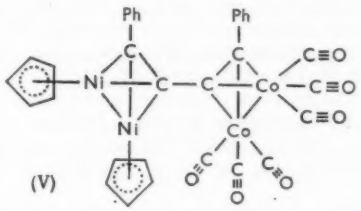
With this idea in mind some typical acetylenic reactions of the dinickel complex (III) were attempted in the hope that only the free triple bond would react. Hydration of the complex (III) failed owing to reduction of mercuric acetate to metallic mercury. Hydrogenation proceeded at room temperature and atmospheric pressure over either Raney nickel or 5% palladised charcoal, but it was impossible to stop hydrogenation sharply at any one stage, and absorption of two mols. of hydrogen gave mixtures of purely organic with organometallic products. The latter were not separated by chromatography on alumina. Reaction of neither phenyl azide nor benzenesulphonyl azide with the complex (III) leads to the expected triazole derivative. However, normal products were obtained by reaction with dicobalt octacarbonyl and with iron tetracarbonyl: the former yields black crystals, $C_{32}H_{20}Co_2Ni_2O_6$, that give dark brownish-green solutions. Infrared absorption at 2070 and 2047 cm.$^{-1}$ indicates terminal carbonyl groups, and the compound evidently has structure (V) in which one triple bond of the diyne has formed a complex



(V)

with nickel and the other with cobalt. Iron tetracarbonyl in boiling ligroin yielded two products that were separated chromatographically. The first was a black solid which gave dark blue solutions in organic solvents. Infrared absorption at 2028 and 1970 cm.$^{-1}$ indicated the presence of terminal carbonyl groups and the analysis corresponded to the formula $(C_5H_5Ni)_2$,PhC:C·C:C·Ph,$Fe_2(CO)_6$. The second product was a black solid giving brown solutions in organic solvents, and its analyses corresponded to the structure $[(C_5H_5Ni)_2$,PhC:C·C:CPh$]_2Fe_2(CO)_6$: it had infrared absorption bands due to carbonyl at 2030, 1988, and 1968 cm.$^{-1}$. Complexes PhC:CPh,$Fe_2(CO)_6$, and $(PhC:CPh)_2Fe_2(CO)_6$ have been prepared by Hubel and Braye,[9] and our two organo-iron-nickel complexes probably have analogous structures.

Experimental

M. p.s of organometallic compounds were obtained in sealed evacuated tubes. Oxygen was determined by Oliver's [10] method. After acid oxidation of organic matter, nickel [11] and cobalt [12] were determined colorimetrically, and iron [13] volumetrically.

Dicyclopentadienyldinickel Dicarbonyl.—This was prepared by an improvement on Fischer and Palm's procedure.[2] Dicyclopentadienenickel (24·5 g.), nickel carbonyl (45 c.c.), and benzene (250 c.c.) were stirred under reflux for 3½ hr. under nitrogen, on a water-bath at 80°. The solvent and excess of nickel carbonyl were removed, and the residue was extracted with boiling ether (400 c.c.). The filtered solution was concentrated and allowed to crystallise. Further crystals were obtained by concentrating the mother-liquors with the addition of low-boiling ligroin, giving black or dark red plates (29·1 g., 74%), m. p. 146—147° (Fischer and Palm reported m. p. 139°) (Found: C, 47·4; H, 3·4; O, 10·7. Calc. for $C_{12}H_{10}Ni_2O_2$: C, 47·5; H, 3·3; O, 10·5%).

Dicyclopentadienyldinickel–Acetylene Complexes.—General method. Dicyclopentadienyldinickel dicarbonyl (I) was refluxed under nitrogen with 10—50% excess of the acetylene in

[9] Hubel and Braye, *J. Inorg. Nuclear Chem.*, 1959, **10**, 250.
[10] Oliver, *Analyst*, 1955, **80**, 593.
[11] "The B.D.H. Book of Organic Reagents," B.D.H., London, p. 44.
[12] Young, "Industrial Inorganic Analysis," Chapman and Hall, London, 1953, p. 79.
[13] Kolthoff and Belcher, "Volumetric Analysis," Interscience Publ. Inc., New York, 1957, Vol. III, p. 623.

toluene for ½—2 hr. The solvent was then evaporated and the excess of acetylene removed at the pump on a steam-bath. The residue was chromatographed on alumina, and the green fraction recrystallised or sublimed, or, if liquid, rechromatographed. This method was employed in the following cases:

(1) Hex-1-yne (4·0 c.c.) and the carbonyl (I) (4 g.) yielded *dicyclopentadienyldinickel–hex-1-yne* (1·51 g., 35%), m. p. 46·5—47° (Found: C, 58·4; H, 5·8. $C_{16}H_{20}Ni_2$ requires C, 58·3; H, 6·1%).

(2) Hex-3-yne (1·0 c.c.) and the carbonyl (I) (1·0 g.) yielded *dicyclopentadienyldinickel–hex-3-yne* as a dark green oil (Found: C, 58·4; H, 6·3%).

(3) Phenylacetylene (3 c.c.) and the complex (I) (1·52 g.) yielded dicyclopentadienyldinickel–phenylacetylene (1·21 g., 69%) as black needles, m. p. 132—133° (Found: C, 62·1; H, 4·8. Calc. for $C_{18}H_{16}Ni_2$: C, 61·8; H, 4·6%).

(4) Diphenylacetylene (1·03 g.) and the carbonyl (I) (0·60 g.) yielded dicyclopentadienyldinickel–diphenylacetylene as black crystals, m. p. 149—150° (1·28 g., 88%) (Found: C, 68·0; H, 5·2%; *M*, 409. Calc. for $C_{24}H_{20}Ni_2$: C, 67·7; H, 4·7%; *M*, 426).

In the following cases variations of the general method were employed:

(1) Acetylene was bubbled through a refluxing solution of the carbonyl (I) in benzene and gave a very small yield of dicyclopentadienyldinickel–acetylene as dark green crystals, m. p. 143—144° (Found: C, 52·9; H, 4·6. Calc. for $C_{12}H_{12}Ni_2$: C, 52·7; H, 4·8%).

(2) But-2-yne (1·5 c.c.), the carbonyl (I) (4·0 g.), and benzene (50 c.c.) were heated in 2 hr. to 130°, in a sealed tube in an atmosphere of carbon dioxide. This yielded a green oil which sublimed at 100°/0·01 mm., yielding black crystals of *dicyclopentadienyldinickel–but-2-yne* (1·95 g., 49%) that on resublimation had m. p. 55° (Found: C, 55·8; H, 5·5. $C_{14}H_{16}Ni_2$ requires C, 55·7; H, 5·4%).

(3) Diphenylbutadiyne (10·1 g., 2·16 mol.), the carbonyl (I) (7·0 g., 1·0 mol.), and benzene (250 c.c.) were refluxed under nitrogen for 6 hr. The mixture, on cooling, was filtered from needles of *tetracyclopentadienyltetranickel–diphenylbutadiyne* (IV), and the filtrate was evaporated. The residue was extracted with boiling ether (150 + 50 c.c.) which left most of the tetranickel complex behind. This together with the first portion was recrystallised from chloroform–ligroin (b. p. 60—80°), yielding black needles (3·2 g.), m. p. 296—297° (Found: C, 62·0; H, 4·6. $C_{36}H_{30}Ni_4$ requires C, 62·0; H, 4·3%). The ether extract was evaporated and the residue chromatographed on alumina. Elution with ligroin (b. p. 40—60°) gave, first, diphenylbutadiyne, then *dicyclopentadienyldinickel–diphenylbutadiyne* that recrystallised from ether–ligroin as black crystals (3·3 g.), m. p. 121° (Found: C, 69·2; H, 4·7. $C_{26}H_{20}Ni_2$ requires C, 69·4; H, 4·5%).

Preparation of Dicyclopentadienyldinickel–Diphenylacetylene from Dicyclopentadienylnickelocene.—Dicyclopentadienylnickel (2·89 g.), diphenylacetylene (2·7 g.), nickel carbonyl (6·0 c.c.), and benzene (70 c.c.) were refluxed for 6 hr. under nitrogen. The benzene and excess of nickel carbonyl were removed and the residue was recrystallised from ether–ligroin, yielding black crystals of dicyclopentadienyldinickel–diphenylacetylene (5·55 g., 85%).

Reactions of Cyclopentadienylnickel–Acetylene Complexes.—Oxidation. A rapid stream of air was bubbled through a solution of dicyclopentadienyldinickel–diphenylacetylene (0·40 g.) and hydrochloric acid (1 c.c.) in ether (20 c.c.) and ethanol (25 c.c.), until, after 5 min., the colour was destroyed. Water was added and the ether layer separated and evaporated, yielding impure diphenylacetylene (0·177 g., 100%) which was recrystallised and had m. p. and mixed m. p. 60°. A solution of tetracyclopentadienyltetranickel–diphenylbutadiyne in chloroform–ethanol gave a 100% yield of diphenylbutadiyne by similar treatment.

Carbon monoxide. A solution of dicyclopentadienyldinickel–diphenylacetylene (10·4 g.) in benzene (400 c.c.) was heated in an autoclave at 110° with 70 atm. of carbon monoxide for 11 hr. On cooling, the solution was pale brown and evaporation gave a pale oil which yielded diphenylacetylene on chromatography. The colourless benzene distillate readily gave a nickel mirror, and reacted vigorously with nitric acid, giving nickel nitrate, and evidently contained most of the nickel as nickel carbonyl.

Reduction. Dicyclopentadienyldinickel–diphenylacetylene (0·50 g.) was reduced with sodium (2 g.) and ethanol (4 c.c.) in liquid ammonia (100 c.c.) in the normal way and gave bibenzyl (0·19 g., 89%), m. p. and mixed m. p. 51—52°.

Dicyclopentadienyldinickel–diphenylacetylene did not react when refluxed for 15 hr. with triphenylphosphine in toluene, or for 18 hr. with pyridine in benzene. This is in contrast

XUM

with dicyclopentadienyldinickel dicarbonyl which gave a 54% yield of tricyclopentadienyltrinickel dicarbonyl [2] when left at room temperature with pyridine in ether for 10 days.

Reaction of dicyclopentadienyldinickel–diphenylbutadiyne with cobalt carbonyl. Cobalt carbonyl (1·6 g.) and dicyclopentadienyldinickel–diphenylbutadiyne (1·0 g.) were refluxed under nitrogen in ether (45 c.c.) for 1 hr. The solvent was removed and the residue crystallised from ether–ligroin yielding black *dicyclopentadienyldinickel–diphenylbutadiyne–dicobalt hexacarbonyl*, m. p. 156—158° (decomp.) (Found: C, 52·3; H, 2·7; O, 13·7; Ni, 16·5; Co, 16·1, $C_{32}H_{20}Co_2Ni_2O_6$ requires C, 52·2; H, 2·7; O, 13·1; Ni, 15·95; Co, 16·0%).

Reaction of dicyclopentadienyldinickel–diphenylbutadiyne with iron tetracarbonyl. The dinickel complex (2·0 g., 3 mol.), iron tetracarbonyl (0·76 g., 1 mol.), and ligroin (100 c.c.; b. p. 80—100°) were refluxed under nitrogen for 3 hr. The solvent was removed and the residue chromatographed on neutralised alumina. Elution with ligroin gave a blue solution which on evaporation gave a black solid (0·12 g.), m. p. 156° (from ligroin). The infrared spectrum and analysis corresponded to a structure $(C_5H_5Ni)_2$,PhC:C·C:CPh,$Fe_2(CO)_6$ (Found: C, 53·1; H, 3·1; O, 12·4; Ni, 16·1; Fe, 15·9. $C_{32}H_{20}Fe_2Ni_2O_6$ requires C, 52·7; H 2·8; O, 13·2; Ni, 16·1; Fe, 15·3%). Further elution with ligroin yielded a brown gum (0·86 g.) which on crystallisation from ligroin yielded black crystals, m. p. 160—161°. The analysis corresponds best to a structure $[(C_5H_5Ni)_2$,PhC:C·C:CPh$]_2Fe_2(CO)_6$ (Found: C, 59·2; H, 3·6; O, 8·6; Ni, 20·4; Fe, 10·2. $C_{58}H_{40}Fe_2Ni_4O_6$ requires C, 59·1; H, 3·4; O, 8·1; Ni, 19·9; Fe, 9·5%).

The author thanks Dr. O. S. Mills for suggesting the work and the University of Sheffield for an Imperial Chemical Industries Research Fellowship. He also thanks the Mond Nickel Co. for gifts of nickel and cobalt carbonyls.

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Sheffield, 10.

[*Received, May 30th*, 1960.]

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116. *A Bisglycerol Tricarbonate.*

By L. Hough and J. E. Priddle.

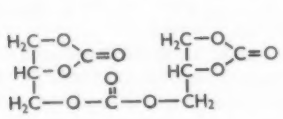
Examination of the infrared spectrum of a crystalline bisglycerol tricarbonate has shown it to be bis(glycerol 1,2-carbonate) 3,3′-carbonate (I). A quantitative evaluation of the relative intensities of the two C=O stretching absorptions of the compound is described. The apparent C=O stretching absorption intensities of propylene carbonate, propane-1,3-diol carbonate, dimethyl carbonate, and diethyl carbonate have also been calculated.

Preparations of a crystalline glycerol carbonate, $(C_9H_{10}O_9)_x$, were patented in 1911 and 1912 by Scheuble and Hochstetter.[1] Of the two methods cited, namely, the reaction of carbonyl chloride with glycerol in an organic base such as pyridine, and the ester-exchange of glycerol with an organic carbonate, the latter was the more convenient. In 1935, similar preparations of the glycerol carbonate were patented.[2] Bruson and Riener [3] re-investigated the ester-exchange by altering the molar ratio of the reagents and, with an excess of glycerol, resinous polycarbonates were obtained.

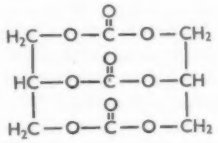
The only attempt to elucidate the structure of Scheuble and Hochstetter's glycerol carbonate was made by Contardi and Ercoli,[4] who assumed the molecular formula to be $C_9H_{10}O_9$. (This molecular formula has now been verified.) On this basis, they considered only two structures, namely, bis(glycerol 1,2-carbonate) 3,3′-carbonate (I), and the rather crowded, cage-like bisglycerol 1,1′:2,2′:3,3′-tricarbonate (II). By comparison with the structure of the known 3-chloropropane-1,2-diol carbonate (III), they preferred the former. They did not, however, consider other isomeric structures such as (IV) and (V). A recent

[1] Scheuble and Hochstetter, B.P. 19,924/1911; *Chem. Zentr.*, 1912, **83**, II, 1756.
[2] Soc. industrielle Vator, F.P. 779,342/1935; *Chem. Abs.*, 1935, **29**, 5460.
[3] Bruson and Riener, *J. Amer. Chem. Soc.*, 1952, **74**, 2100.
[4] Contardi and Ercoli, *Gazzetta*, 1934, **64**, 522.

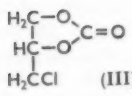
examination [5] of the formation of carbonate derivatives of methyl glycopyranosides has revealed that five-membered cyclic carbonates are formed in preference to six-membered cyclic carbonates because of the more favourable situation of a trigonal carbon atom in a five- rather than in a six-membered ring. By analogy, glycerol would be expected to give a carbonate of structure (I) in preference to (IV) and (V).



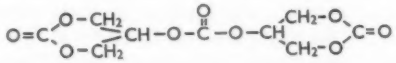
(I)



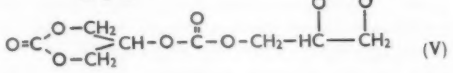
(II)



(III)



(IV)



(V)

Studies of the infrared absorption spectra of some carbohydrate carbonates [6] and other simpler organic carbonates [7] have revealed the usefulness of the C=O stretching frequency in structural work. Thus five-membered organic cyclic carbonates showed a C=O vibration absorption maximum near 1800 cm.$^{-1}$, whereas with linear carbonates the maximum appeared close to 1760 cm.$^{-1}$. As expected by comparison with cyclic lactones and ketones, the six-membered propane-1,3-diol carbonate also showed a C=O vibration maximum at 1760 cm.$^{-1}$.

The infrared absorption spectrum of bisglycerol tricarbonate (potassium bromide disc) showed C=O stretching absorptions at 1800 and 1760 cm.$^{-1}$, the former being the more intense. This ruled out structures (II) and (IV) since they do not contain five-membered cyclic carbonate groups. In order to establish the ratio of open to cyclic carbonate groups and so distinguish between structures (I) and (V), the C=O stretching intensities at 1800 and 1760 cm.$^{-1}$ were examined quantitatively.

Methods have been given for calculating the difference between the true integrated absorption intensity and the experimentally determined value; [8] an increment of 2—3% was involved. R. N. Jones and his co-workers [9] have shown that the C=O stretching absorption intensities of similar carbonyl groups in different steroid environments are approximately the same. Antia [10] has used this principle to prove the structure of 1,3,4-tri-*O*-acetyl-α-D-xylopyranose.

It was appropriate therefore to examine the infrared spectra of propylene carbonate and diethyl carbonate as model compounds in order to determine the ratio of apparent integrated C=O stretching absorption intensities of the five-membered cyclic-carbonate and open-carbonate groups.

The apparent integrated C=O stretching absorption intensity of propylene carbonate was 4·7 intensity units (*c* 1·61 in $CHCl_3$) (one intensity unit = 1×10^4 mole^{-1} l. cm.$^{-2}$), and the value for diethyl carbonate was 4·0 intensity units (*c* 1·4 in $CHCl_3$). The ratio of these intensities is 1·2 : 1. For bisglycerol tricarbonate, the ratio of the intensity of the 1800 cm.$^{-1}$ peak to that of the 1760 cm.$^{-1}$ peak was 2·39 : 1. Hence the presence of

[5] Hough and Priddle, *Chem. and Ind.*, 1959, 1600.
[6] Hough, Priddle, Theobald, Barker, Douglas, and Spoors, *Chem. and Ind.*, 1960, 148.
[7] Angell, *Trans. Faraday Soc.*, 1956, **52**, 1178; Hales, Idris Jones, and Kynaston, *J.*, 1957, 618; Gatehouse, Livingstone, and Nyholm, *J.*, 1958, 3137; Sarel, Pohoryls, and BenShoshan, *J. Org. Chem.*, 1959, **24**, 1873.
[8] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72; Cabana and Sandorfy, *Spectrochim. Acta*, 1960, **16**, 335.
[9] R. N. Jones, Ramsay, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80.
[10] Antia, *J. Amer. Chem. Soc.*, 1958, **80**, 6138.

five-membered cyclic groups and open-carbonate groups in the ratio of 2·0 : 1 was revealed, thus providing proof for the bis(glycerol 1,2-carbonate) 3,3′-carbonate structure (I).

The value of the integrated C=O absorption intensity of propane-1,3-diol carbonate was 5·3 intensity units (*c* 1·38 in $CHCl_3$), which clearly ruled out structure (V).

The validity of the method employed was confirmed by a similar calculation using data obtained for methyl 4,6-di-*O*-methoxycarbonyl-α-D-mannopyranoside 2,3-carbonate,[5] in which the ratio of the intensities of the 1800 and the 1760 cm.$^{-1}$ peak was 1 : 1·51. By using the C=O stretching intensity of propylene carbonate in conjunction with that of dimethyl carbonate [3·7 intensity units (*c* 1·65 in $CHCl_3$)], a ratio of 1·9 : 1 was found for the number of *O*-methoxycarbonyl groups to cyclic carbonate groups.

Experimental

Infrared Absorption Spectra.—The spectra were obtained by using a Unicam S.P. 100 double-beam infrared spectrometer with a rock-salt prism. A potassium bromide disc technique (0·5 mg. of compound in 500 mg. of KBr) was used for the glycerol carbonate, but in all other cases chloroform solutions were used.

Bis(glycerol 1,2-carbonate) 3,3′-Carbonate.[1,2]—This was prepared by heating glycerol (20 g.) with diphenyl carbonate (17 g.) at 130°. The product (12 g.), crystallised from pyridine–ethanol and recrystallised from acetone, had m. p. 151—152°, $\nu_{max.}$ (C=O stretching) 1800 and 1760 cm.$^{-1}$ [Found: C, 41·0; H, 4·0%; *M* (Rast), 274. Calc. for $C_9H_{10}O_9$: C, 40·9; H, 4·0%; *M*, 262).

Propane-1,3-diol Carbonate.—The method of Carothers and Van Natta [11] was used. Metallic sodium (0·2 g.) was dissolved in a mixture of propane-1,3-diol (30·4 g.) and diethyl carbonate (57 ml.), and the solution heated at 120°, rising to 180° in 3 hr. The propane-1,3-diol carbonate (22 g.) obtained after recrystallisation from ether had m. p. 48°, $\nu_{max.}$ (C=O stretching) 1760 cm.$^{-1}$ (Found: C, 46·8; H, 5·9. Calc. for $C_4H_6O_3$: C, 47·1; H, 5·9%).

Commercial preparations of dimethyl carbonate, diethyl carbonate, and propylene carbonate were purified by fractional distillation. They had $\nu_{max.}$ (C=O) at 1760, 1760, and 1800 cm.$^{-1}$, respectively.

Calculation of Integrated Absorption Intensities.—The apparent integrated absorption intensity (*A*) of a peak is given by the equation:

$$A = \frac{1}{cl}\int \log_e\left(\frac{y_0}{y}\right)_\nu d\nu$$

where *c* is the concentration in mole l.$^{-1}$, *l* the path length in cm., and y_0 and y are the transmission of the solvent and of the compound plus solvent, respectively, at the required frequency ν.

In order to calculate the relative absorption intensities of the overlapping C=O peaks of the glycerol carbonate it was assumed that the peaks were symmetrical and that the frequencies of the two maxima were 1760 and 1800 cm.$^{-1}$. The movement of these maxima from their true frequencies by the overlapping of the peaks was insignificant. A graph of $\log_e y_0/y$ against ν was plotted, and the individual peak areas were calculated by correcting for the overlap. (Where the potassium bromide disc technique was used, y_0 was estimated from a horizontal portion of the infrared spectrum where the absorption due to the compound was very small over *ca.* 100 cm.$^{-1}$.)

The smaller peak did not extend significantly to frequencies greater than that of the maximum of the larger peak at 1800 cm.$^{-1}$; hence the area above this frequency was taken as the half-peak area. The values of $\log_e y_0/y$ for the larger peak at frequencies less than 1800 cm.$^{-1}$ were then plotted by using symmetry. Since $y_1 = y_0 + y - y_2$, where y, y_1 and y_2 represent approximately the transmissions at any particular frequency for the complete curve, the smaller peak, and the larger peak, respectively, values for y_1 below 1760 cm.$^{-1}$ could be calculated. A plot of these values against frequency enabled the half-peak area to be determined.

[11] Carothers and Van Natta, *J. Amer. Chem. Soc.*, 1930, **52**, 314.

The ratio of the intensity of the peaks at 1800 cm.$^{-1}$ and 1760 cm.$^{-1}$ was therefore given by

$$2\int_{1800}^{\infty} \log_e\left(\frac{y_0}{y_2}\right)_\nu d\nu \Big/ 2\int_0^{1760} \log_e\left(\frac{y_0}{y_1}\right)_\nu d\nu$$

All integrals were evaluated graphically.

We thank Drs. T. H. K. Barron and W. J. Dunning and Mr. R. C. Seymour for helpful advice, Dr. R. S. Theobald for his continued interest, and the Department of Scientific and Industrial Research for a grant to J. E. P.

THE UNIVERSITY, BRISTOL. [*Received, June 28th*, 1960.]

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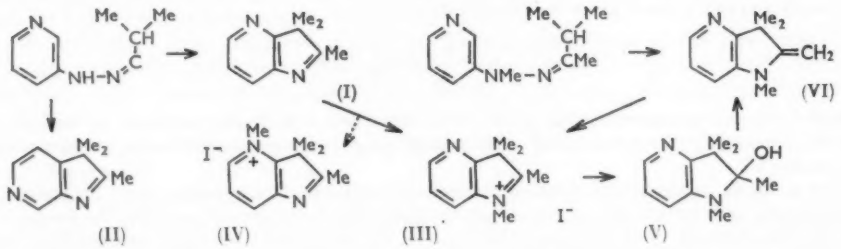
117. *Diazaindenes and Their Quaternary Salts. Part II.*[1] *The Cyclisation of Isopropyl Methyl Ketone 3-Pyridylhydrazone.*

By G. E. FICKEN and J. D. KENDALL.

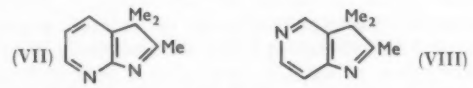
Isopropyl methyl ketone 3-pyridylhydrazone undergoes the Fischer indole synthesis to give a base to which the 1,4-diazaindene structure (I) is assigned. With methyl iodide it gives the 1-methiodide, which has also been synthesised by way of 1,3,3-trimethyl-2-methylene-1,4-diazaindane (VI). The methiodide yields cyanine dyes, the light absorption of which is discussed.

PART I of this series[1] described the preparation of a diazaindene by cyclisation of isopropyl methyl ketone 2-pyridylhydrazone catalysed by zinc chloride. We have now found that the isomeric 3-pyridylhydrazone also undergoes the Fischer indole synthesis to give another diazaindene. This was obtained as a hygroscopic liquid which has been characterised as its picrate and methiodide.

This base might be the 1,4- (I) or the 1,6-diazaindene (II). Evidence that it is the former is, however, provided by the infrared spectrum.



It is probably the CH out-of-plane deformation vibrations in pyridines that causes strong absorption in the 900—700 cm.$^{-1}$ region, the position of the bands depending largely on the number of adjacent hydrogen atoms in the ring, as with benzene derivatives.[2]



Thus, a diazaindene (I) would be expected to resemble, not only the 1,7-diazaindene (VII) and 2,3-disubstituted pyridines, but also *vic*-trisubstituted benzenes. On the other hand, a diazaindene (II) should be comparable with the 1,5-diazaindene (VIII), 3,4-disubstituted

[1] Part I, Ficken and Kendall, *J.*, 1959, 3202.
[2] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn., 1958, p. 280.

pyridines, and *as*-trisubstituted benzenes. Some relevant data are given in Table 1, including the two compounds (V) and (VI), the preparation of which is discussed below. These, and the diazaindene to which they are related, show two strong bands in the infrared region under discussion. Although it is not possible to say which of the two is the result of a CH out-of-plane vibration, both bands are in each case consistent with a 2,3-disubstituted pyridine structure; 3,4-disubstitution would appear to be excluded. The base is therefore on this evidence assigned the 1,4-diazaindene structure (I).

This conclusion is in agreement with the rather limited evidence that electrophilic attack on a pyridine possessing an *ortho,para*-directing 3-substituent leads to substitution in the 2- in preference to the 4-position.[3] It is of interest that a Skraup reaction on 3-aminopyridine apparently gives only 1,5-naphthyridine (*i.e.*, 2-substitution).[4] As regards Fischer syntheses on 3-hydrazinopyridines, Clemo and Holt [5] have prepared a tetrahydrocarboline by this method, but here cyclisation on to $C_{(4)}$ was forced by the presence of a 2-methyl group. The only other reported examples involved 2-chloro-5-hydrazinopyridine, where Fischer syntheses were assumed to lead to 1,4-diazaindenes.[6]

We have shown [1] that both of the methiodides of 2,3,3-trimethyl-3*H*-1,7-diazaindene (VII) have a reactive 2-methyl group. In the present case, however, only the 1-methiodide (III) could, the reactive species being the methylene base (VI) (cf. Mills and Raper [7]). The 4-methiodide (IV) would not activate the 2-methyl group, owing to the impossibility of forming a methylene base possessing a *meta*-quinonoid pyridine ring. In fact the methiodide obtained by quaternisation of the base (I) possessed a very reactive methyl

TABLE 1. *Strong absorption bands in the* CH *deformation region* ($cm.^{-1}$).

Benzenes [a]			
1,2,3-Trisubst.	780—760	1,2,4-Trisubst.	825—805
Pyridines			
2,3-Dimethyl [b]	787	3,4-Dimethyl [b]	839, 821
2-Acetamido-3-methyl	803		
2,3,3-*Trimethyl*-3H-*diazaindenes*			
1,7-Diaza (VII)	807	1,5-Diaza [c] (VIII)	842

Diazaindene (I) 813, 786. Compound (V) 802, 783. Compound (VI) 794, 776.

[a] West, "Chemical Applications of Spectroscopy," Interscience Publ. Inc., New York, 1956, p. 391. [b] Coulson, Cox, Herington, and Martin, *J.*, 1959, 1934. [c] Unpublished work.

TABLE 2. *Light absorption of dyes* [$\lambda_{max.}$ (Å); *and* log ε *in parentheses*].

	Obs.	Calc.	Deviation	Deviation of 1,7-diazaindene dye
Dye (IX)	5580 (4·49)	5770	190	140
Nucleus (A) in (X)				
(1) 1,3,3-Trimethyl-3*H*-indole-2	5440 (5·05)	5455	15	15
(2) 3-Methyl-2-benzoxazole	5030 (4·74)	5140	110	120
(3) 3-Methyl-2-benzothiazole	5350 (4·99)	5510	160	155
(4) 1-Methyl-2-quinoline	5475 (5·00)	5745	270	305
(5) 1-Methyl-4-quinoline	5775 (4·91)	6255	480	515

group, and cyanines were readily obtained in good yield by using the usual reagents. The resulting structure (III) was proved by synthesis of the identical methiodide by addition of hydrogen iodide to the methylene base (VI), obtained by cyclisation of isopropyl methyl ketone *N*-methyl-*N*-3-pyridylhydrazone by zinc chloride.

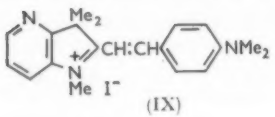
In attempts to reconvert the methiodide (III) into the methylene base (VI) by aqueous

[3] (*a*) Albert, "Heterocyclic Chemistry," University of London Athlone Press, 1959, p. 64; (*b*) Schofield, *Quart. Rev.*, 1950, **4**, 382.
[4] Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081.
[5] Clemo and Holt, *J.*, 1953, 1313.
[6] Deutsche Gold und Silberscheideanstalt, B.P. 259,982/1925; cf. Takahashi, Saikachi, Goto, and Shimamura, *J. Pharm. Soc. Japan*, 1944, **64**, No. 8A, 7; *Chem. Abs.*, 1951, **45**, 8529.
[7] Mills and Raper, *J.*, 1925, **127**, 2466.

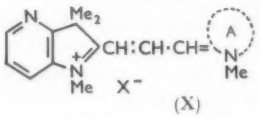
alkali, the product obtained initially was the pseudobase (V), which however readily lost water on gentle heating to give the methylene base.

Although the 4-methiodide (IV) could not be isolated, some was probably formed during the quaternisation of base (I), as the yield of the 1-methiodide was at best a little over 50%. This is in sharp contrast, however, to the behaviour of the isomeric 1,7- and 1,5-diazaindene. The former has been estimated to give <10% of 1-methiodide on quaternisation,[1] and the latter also quaternises almost exclusively on the pyridine nitrogen atom. The predominant quaternisation of the 1,7-diazaindene on $N_{(7)}$ was ascribed to the considerably greater basicity of the pyridine than of the pyrrolenine nitrogen atom. Since a similar disparity would be expected in any diazaindene containing one nitrogen in each ring, some other factor must be at work in the case of (I). The most obvious explanation appears to be that only in (I) would there be any steric hindrance to quaternisation on the pyridine nitrogen, owing to the *gem*-dimethyl group at position 3. This appears to provide additional evidence for formulation of the base as a 1,4- rather than a 1,6-diazaindene.

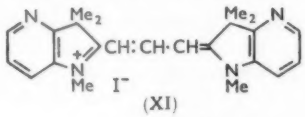
Light Absorption of the Dyes.—The cyanines and merocyanines prepared from the methiodide (III) proved, as expected, very similar in their light absorption to the isomers obtained from the 1,7-diazaindene 1-methiodide.[1] Table 2 gives the absorption data for the styryl dye (IX) and for a series of trimethincyanines (X), arranged in order of increasing basicity of (A). The Brooker " deviations " are derived as described in Part I,[1] the requisite symmetrical dye being (XI). Some figures pertaining to the corresponding



(IX)



(X)



(XI)

$\lambda_{max.}$ 5440 Å (log ε 5·14)

1,7-diazaindene dyes, taken from Part I,[1] are included for comparison. For the more strongly basic nuclei (A), *viz.*, dyes (4) and (5), the deviations for dyes (X) are somewhat less than for the related 1,7-diazaindene dyes, whilst the reverse is true for dye (IX). These facts indicate that, following Brooker and Sprague's arguments,[8] $N_{(1)}$ is slightly more basic in (I) than in the 1,7-diazaindene (VII).

Experimental

Isopropyl Methyl Ketone 3-Pyridylhydrazone.—3-Aminopyridine (91 g.) was diazotised and reduced with stannous chloride by Räth's method.[9] The resulting stannichloride was stirred with isopropyl methyl ketone (200 ml.) and excess of aqueous sodium hydroxide, and the solution was continuously extracted with ether. Removal of the solvent and excess of ketone from the dried (K_2CO_3) extract left a thick brown oil (87 g.) which was used immediately for the preparation of the diazaindene. Distillation of this oil at 180—200°/20 mm. gave *isopropyl methyl ketone 3-pyridylhydrazone*, which formed colourless plates, m. p. 89—90° from cyclohexane (Found: C, 67·5; H, 8·2. $C_{10}H_{15}N_3$ requires C, 67·8; H, 8·5%). The crystals rapidly became brown in the air.

2,3,3-Trimethyl-3H-1,4-diazaindene (I).—The crude hydrazone (68 g.) was heated with anhydrous zinc chloride (1·0 g.), the temperature (external) being raised during 1½ hr. from 195° to 220°. Fractionation of the thick brown residue gave a first fraction (20·3 g.), b. p. 62°/0·8 mm. to 86°/1·0 mm., followed by a fraction (7·5 g.) of b. p. 89—92°/0·8 mm. The latter solidified on cooling and consisted largely of 3-aminopyridine; the picrate, yellow needles from 2-methoxyethanol, had m. p. and mixed m. p. with 3-aminopyridine picrate 200—201° (Found: N, 21·9. Calc. for $C_{11}H_9N_5O_7$: N, 21·7%). The first fraction from the distillation

[8] Brooker and Sprague, *J. Amer. Chem. Soc.*, 1945, **67**, 1869.
[9] Räth, *Annalen*, 1931, **486**, 103.

was refractionated, to give material, b. p. 103—107°/16 mm. (14·4 g.), from which **2,3,3-*trimethyl*-3H-1,4-*diazaindene*** was obtained as a colourless hygroscopic liquid, b. p. 112°/19 mm., n_D^{15} 1·5432 (Found: N, 17·6, 17·8. $C_{10}H_{12}N_2$ requires N, 17·5%). The ***picrate***, yellow plates from ethanol, had m. p. 160° (Found: C, 49·4; H, 4·1. $C_{16}H_{15}N_5O_7$ requires C, 49·4; H, 3·9%).

The diazaindene (2·45 g.) was refluxed in ethanol (10 ml.) with methyl iodide (2·0 ml.) for 40 min., by which time crystals had separated. These were filtered off after refrigeration and washed successively with a little ice-cold ethanol and acetone. The 1-methiodide (III) (2·59 g.) formed colourless needles, m. p. 252—253° (decomp.), from ethanol (Found: C, 44·2; H, 5·2; I, 41·95; N, 9·0. $C_{11}H_{15}IN_2$ requires C, 43·7; H, 5·0; I, 42·0; N, 9·3%).

N-Methyl-N-3-pyridylhydrazine.—3-(Methylnitrosoamino)pyridine [10] was reduced in 85% yield with lithium aluminium hydride, as described in Part I; the b. p. was 112°/1·2 mm. to 118°/1·0 mm. Plazek *et al.*[10] give b. p. 191°/11 mm.

1,3,3-*Trimethyl*-2-*methylene*-1,4-*diazaindane*.—*N*-Methyl-*N*-3-pyridylhydrazine (18·6 g.) and isopropyl methyl ketone (20 ml.) were warmed for 2½ hr. on the steam-bath with acetic acid (0·5 ml.). Volatile material was removed at 100°/16 mm., and the residual yellow-brown oil was heated with anhydrous zinc chloride (0·5 g.), a vigorous reaction occurring at 190°. Heating was continued for 20 min., during which the temperature was raised to 210°, and the thick brown residue was distilled. No sharp boiling fraction could be obtained, but the material (11·4 g.) boiling between 106° and 130°/19 mm. was collected and treated in propan-2-ol (110 ml.) with freshly distilled hydriodic acid (*d* 1·70; 9·6 ml.). The crystals which separated slowly were collected and washed successively with a little cold propan-2-ol and ether to give the 1-methiodide (III) (5·33 g.), m. p. 252—253° (decomp.), undepressed by the product of quaternisation of the diazaindene (I). The infrared spectra of the two samples were identical, and they yielded styryl dyes (see below) which were identical in m. p. and mixed m. p. and in their light absorption (visible and infrared). A fraction (5·2 g.), b. p. 132—160°/18 mm., from the distillation, when similarly treated with hydriodic acid, gave a further quantity (0·65 g.) of the methiodide (combined yield based on the pyridylhydrazine, 13%).

The methiodide (6·02 g.) was warmed to about 40° with N-sodium hydroxide (50 ml.) for a few minutes. After cooling in ice, the solid was collected, washed with a little cold water, and crystallised from ethyl acetate. **2-*Hydroxy*-1,2,3,3-*tetramethyl*-1,4-*diazaindane*** (V) (1·97 g.) was obtained as colourless crystals, m. p. 91°, which fairly rapidly became pink and liquefied when exposed to the air (Found: N, 14·8. $C_{11}H_{16}N_2O$ requires N, 14·9%). Evaporation of an ethyl acetate solution of this compound to dryness on the steam-bath gave an oil which did not solidify when strongly cooled. An ethereal solution of this oil was dried (K_2CO_3) and distilled, **1,3,3-*trimethyl*-2-*methylene*-1,4-*diazaindane*** (VI) being obtained as a pale yellow liquid, b. p. 125°/18 mm., n_D^{20} 1·5800, which very rapidly became red in the air (Found: C, 75·4; H, 8·0. $C_{11}H_{14}N_2$ requires C, 75·8; H, 8·1%).

Preparation of Dyes from the Methiodide (III).—(a) *Trimethincyanines.* These *dyes* were prepared by reaction of the quaternary salt (III) with an ω-ethylthiovinyl or ω-acetanilidovinyl heterocyclic methiodide in pyridine. The symmetrical *dye* (XI) was obtained by reaction of the methiodide (III) with ethyl orthoformate in pyridine. The results are summarised in Table 3, yields referring respectively to the crude and once recrystallised dyes.

TABLE 3. (A) **(1,3,3-*Trimethyl*-3H-1,4-*diazaindene*-2)-*trimethincyanine iodides*** (X).

Dye	M. p.	Yield (%) *	Solvent [a] (ml./g.)	Appearance	Formula	Found (%)	Reqd. (%)
(XI)	326 [d]	56; 24	E(35)	Hexagonal golden plates	$C_{23}H_{27}IN_4$	I, 26·15	26·1
1 [b]	296 [d]	78; 49	M(65)	Red plates, blue reflex	$C_{24}H_{29}ClN_2O_4$ [c]	N, 9·0	9·2
2	238	53; 36	EW	Red needles	$C_{21}H_{22}IN_3O$	I, 27·5	27·6
3	260 [d]	59; 40	M(30)	Green prisms	$C_{21}H_{22}IN_3S$	I, 26·85	26·7
4	286—287 [d]	70; 42	M(55)	Green prisms	$C_{23}H_{24}IN_3$	I, 26·8	27·0
5	299	28; 25	M(75)	Green needles	$C_{23}H_{24}IN_3,H_2O$	I, 26·1	26·0

[a] E = Ethanol, M = Methanol, W = Water. [b] These numbers refer to Table 2. [c] Perchlorate. [d] With decomp. * See text.

(b) *Dimethinmerocyanines and styryl dye.* The methiodide (III) (0·71 g.) and 5-ethoxymethylene-3-ethyl-2-thiothiazolid-4-one (0·51 g.) were refluxed together in ethanol (5·0 ml.) containing triethylamine (0·4 ml.) for 1 hr. The solid (0·42 g.) which separated on cooling

[10] Plazek, Marcinikow, and Stammer, *Rocznicki Chem.*, 1935, **15**, 365; *Chem. Abs.*, 1936, **30**, 1377.

XUM

crystallised from methanol (70 ml.), to give 5-(1,2-*dihydro*-1,3,3-*trimethyl*-3H-1,4-*diazainden*-2-*ylidene*)*ethylidene*-3-*ethyl*-2-*thiothiazolid*-4-*one* (0·33 g.), red prisms, m. p. 228° (Found: S, 18·3. $C_{17}H_{18}N_2OS_2$ requires S, 18·6%). $\lambda_{max.}$ 4850 Å (log ε 4·86). The methiodide (III) (0·75 g.), 3-methyl-1-phenylpyrazol-5-one (0·45 g.), pyridine (5·0 ml.), and ethyl orthoformate (0·8 ml.) were refluxed together for 45 min. The solid (0·70 g.) which separated when the solution was cooled and diluted with ethanol crystallised from methanol (80 ml.), to give 4-(1,2-*dihydro*-1,3,3-*trimethyl*-3H-1,4-*diazainden*-2-*ylidene*)*ethylidene*-3-*methyl*-1-*phenylpyrazol*-5-*one* (0·60 g.), red plates with a silver reflex, m. p. 220—221° (Found: C, 71·4; H, 6·2; N, 14·7. $2C_{22}H_{22}N_4O,H_2O$ requires C, 71·9; H, 6·3; N, 15·2%), $\lambda_{max.}$ 4630 Å (log ε 4·70).

The methiodide (III) (0·30 g.) and *p*-dimethylaminobenzaldehyde (0·20 g.) were refluxed for 1 hr. in ethanol (5·0 ml.) containing 1 drop of piperidine. The resulting solution was cooled and treated with a concentrated aqueous solution of potassium iodide to precipitate 3,3-*dimethyl*-2-p-*dimethylaminostyryl*-3H-1,4-*diazaindene* 1-*methiodide* (IX) (0·29 g.), green plates, m. p. 268°, from water (Found: C, 55·1; H, 5·6; I, 28·7. $C_{20}H_{24}IN_3$ requires C, 55·4; H, 5·6; I, 29·3%).

Infrared Spectra.—These were measured on an Infracord spectrophotometer, model 137, compounds (I) and (VI) as liquids, the others as Nujol mulls.

2,3,3-*Trimethyl*-3H-1,4-*diazaindene* (I): 2950m, 1605m, 1580w, 1560m, 1458m, 1428w, 1412s, 1380w, 1360w, 1292m, 1272w, 1246m, 1180s, 1152w, 1110m, 1100m, 1036w, 995w, 939w, 870w, 813s, 786s cm.$^{-1}$.

2,3,3-*Trimethyl*-3H-1,5-*diazaindene* (VIII): 3400w, 1880w, 1635w, 1600m, 1560s, 1500w, 1410m, 1326w, 1252m, 1214m, 1160m, 1094m, 1024m, 990m, 967w, 942m, 934m, 877s, 842s, 823w, 799w, 784w.

2,3,3-*Trimethyl*-3H-1,7-*diazaindene* (VII): 1560s, 1400s, 1296w, 1266m, 1210m, 1144w, 1120w, 1082w, 1035w, 992w, 952w, 934w, 875m, 807s, 722m, 695m.

2-*Hydroxy*-1,2,3,3-*tetramethyl*-1,4-*diazaindane* (V): 3200s, 2640w, 2530w, 1950w, 1870w, 1780w, 1730m, 1670m, 1610s, 1595s, 1450s, 1320s, 1288m, 1244m, 1222m, 1192s, 1162m, 1124s, 1102s, 1048m, 1020w, 954w, 930s, 901m, 802s, 783s, 682m.

1,3,3-*Trimethyl*-2-*methylene*-1,4-*diazaindane* (VI): 3120w, 3030m, 1730m, 1670s, 1610s, 1595w, 1488m, 1462s, 1436w, 1388m, 1368w, 1336s, 1316s, 1266m, 1208w, 1196m, 1156s, 1130m, 1084w, 1044m, 952w, 940m, 892w, 794s, 776s, 689w.

We thank Mr. L. R. Brooker for the light absorption data, and Miss J. Connor and Miss J. Bond for the microanalytical results.

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118. *Some Isomeric Amido- and Amino-derivatives of* 9-*Methyl-* *and* 9,10-*Dimethyl-anthracene.*

By A. H. BECKETT and R. G. LINGARD.

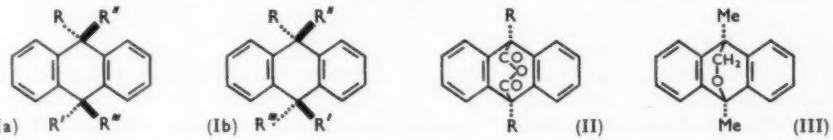
The preparation and stereochemistry of some 9,10-dihydro-9-methyl- and 9,10-dihydro-9,10-dimethyl-anthracene derivatives (9,10-dicarboxylic acid and their amides and esters) are reported.

DURING our work on *meso*-substituted dihydroanthracenes with potential analgesic activity, the compounds (I; R, R′ = H or Me; R″ = CH_2OH or $CH_2{\cdot}CO_2Alk$; R‴ = CH_2Y) were required in which Y is a basic group present in known analgesics, *e.g.*, morpolino or dimethylamino. The preparation of such compounds in which R = R′ = H has been reported elsewhere.[1]

Dimethylanthracene Series (I; R = R′ = Me).—*cis*- and *trans*-9,10-Dihydro-9,10-dihydroxy-9,10-dimethylanthracene were isolated from the ether-soluble and the ether-insoluble fraction respectively obtained by reaction of methylmagnesium iodide with anthraquinone. The infrared spectra of chloroform solutions of the isomers showed

[1] Beckett and Mulley, *J.*, 1955, 4159.

differences that could not all be attributed to the solvent of crystallisation of the *trans*-isomer. The infrared spectrum of the *cis*-isomer in chloroform solution was identical with that of the *cis*-diol prepared stereospecifically by reducing 9,10-epidioxy-9,10-dimethylanthracene [2] with lithium aluminium hydride.



The isomers gave the same dimethyl ether (I; R = R′ = Me, R″ = R‴ = OMe) on treatment with mineral acid in methanol–benzene; [3] a similar result was apparently obtained by Pinazzi on etherification of *cis*- and *trans*-9,10-dihydro-9,10-dihydroxy-9,10-diphenylanthracene.[4] Intermediate carbonium-ion formation would permit the sterically more favoured dimethyl ether to be formed from either diol.

Treatment of 9,10-dihydro-9,10-dimethoxy-9,10-dimethylanthracene with sodium in ether, followed by carboxylation, gave essentially pure dicarboxylic acid, in contrast to the mixture of mono- and di-carboxylic acids resulting from similar treatment of anthracene or 9-methylanthracene.[5] Isolation of the *cis*-dicarboxylic acid (Ia; R = R′ = Me, R″ = R‴ = CO_2H) before dehydration improved the previous yield [6] of the anhydride (II; R = R′ = Me). The anhydride was converted into the *cis*-morpholide acid * (Ia; R = R′ = Me, R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$) by boiling morpholine.[7] This gave a methyl ester that with lithium aluminium hydride yielded the alcohol (Ia or b; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = H) by an unusual type of hydrogenolysis. With this reagent the *cis*-dimethylamide ester (Ia; R = R′ = Me, R″ = CO_2Me, R‴ = $CO{\cdot}NMe_2$) gave a small amount of the expected dimethylaminomethyl derivative (R‴ = $CH_2{\cdot}NMe_2$) but chiefly lost the amide group to give the alcohol (I; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = H); a compound to which the provisional formula (III) has been assigned was also isolated in small yield.

Since hydrogenolyses with lithium aluminium hydride of amides to aldehydes occur more readily with tertiary than with primary amides,[8] the primary amide ester (Ia; R = R′ = Me, R″ = CO_2Me, R‴ = $CO{\cdot}NH_2$) was prepared by treatment of the anhydride (II; R = R′ = Me) with aqueous ammonia and esterification of the product with diazomethane. The *cis*-amide ester was reduced with lithium aluminium hydride, giving a good yield of the amino-alcohol (Ia; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = $CH_2{\cdot}NH_2$), which with formaldehyde–formic acid gave the desired *cis*-dimethylamino-alcohol (R‴ = $CH_2{\cdot}NMe_2$). Since this dimethylamino-alcohol was recovered unchanged after treatment under conditions which caused hydrogenolysis of the *cis*-dimethylamide ester (Ia; R = R′ = Me, R″ = CO_2Me, R‴ = $CO{\cdot}NMe_2$), this base is probably not an intermediate in the hydrogenolysis.

9-Methylanthracene Series (I; R = Me, R′ = H).—Immediate acidification after dissolution of 9,10-dihydro-9-methylanthracene-*cis*-9,10-dicarboxylic anhydride [6] (II; R = Me, R′ = H) in boiling 10% sodium hydroxide solution yielded the substantially pure *cis*-diacid. Acidification after the alkaline solution had been boiled for 3 hours gave

* In this and similar cases throughout this paper a prefix *cis* or *trans* refers to the relation of the carboxyl groups or modified carboxyl groups to one another.

[2] Willemart, *Bull. Soc. chim.*, 1938, **5**, 556.
[3] Bachmann and Chemerda, *J. Org. Chem.*, 1939, **4**, 583.
[4] Pinazzi, *Compt. rend.*, 1946, **223**, 1150.
[5] Beckett and Lingard, *J.*, 1959, 2409.
[6] Beckett, Lingard, and Mulley, *J.*, 1953, 3328.
[7] Mulley, Thesis, London, 1955.
[8] Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, Chapter 10.

the pure *trans*-diacid which yielded less of the *cis*-anhydride when heated with acetic anhydride. The isomeric acids gave the corresponding dimethyl esters with diazomethane.

The *cis*-dicarboxylic anhydride[6] (II; R = R′ = H) dissolved in cold aqueous morpholine to give the known *cis*-acid amide[1] (Ia; R = R′ = H, R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$) almost quantitatively. Under similar conditions, 9,10-dihydro-9-methylanthracene-*cis*-9,10-dicarboxylic anhydride (II; R = Me, R′ = H) gave a substantially pure morpholide acid which was allocated the *cis*-amide acid configuration (Ia; R = Me, and R′ = H, or *vice versa*; R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$) because slower inversion of configuration under alkaline conditions would be expected for this compound than for the morpholide acid (Ia) where R = R′ = H. Reduction of the methyl ester (isomer A) (Ia; R = Me, R′ = H, R″ = CO_2Me, R‴ = $CO{\cdot}NC_4H_8O$) with lithium aluminium hydride gave the amino-alcohol (R″ = $CH_2{\cdot}OH$) in good yield, which supports the configuration assigned to the amide acid.

Treating the anhydride (II; R = Me, R′ = H) with acid in methanol yielded one of the two possible *cis*-acid esters; this gave the *cis*-dimethyl ester (see above) on treatment with diazomethane. The *cis*-acid ester was converted (by treatment with purified thionyl chloride under mild conditions)[9] into the ester acid chloride, and this with morpholine in ether gave one, stereochemically almost pure morpholide ester (isomer B). Since this isomer is probably a *cis*-morpholide ester[1] and had an infrared spectrum in chloroform solution which differed from that of its isomer A, it appears that treatment of the *cis*-dicarboxylic anhydride with either aqueous morpholine or acid methanol gives the 9-carboxylic acid in both cases. As an unsymmetrical aliphatic anhydride gives in major yield that isomer which has the acidic group adjacent to the more branched α-carbon atom,[10] the structures can be deduced with some certainty. Moreover, the anhydride would be expected to undergo preferential nucleophilic attack at the carbon atom of the carbonyl group attached to the CH, owing to the $+I$ effect of the methyl group. The isomeric morpholide esters A and B are therefore assigned the structures (Ia; R = Me, R′ = H) in which R″ = CO_2Me, R‴ = $CO{\cdot}NC_4H_8O$ and R″ = $CO{\cdot}NC_4H_8O$, R‴ = CO_2Me, respectively. Reduction of isomer B with lithium aluminium hydride, in contrast with the similar reduction of the *cis*-morpholide ester where R = R′ = Me, gave a substantial yield of crude base, also supporting[1] the assignment of the *cis*-morpholide ester configuration; the pure morpholide alcohol (Ia; R = Me, R′ = H, R″ = $CH_2{\cdot}NC_4H_8O$, R‴ = $CH_2{\cdot}OH$) could be isolated only in rather low yield.

Experimental

cis- *and* trans-9,10-*Dihydro*-9,10-*dihydroxy*-9,10-*dimethylanthracene* (I; R = R′ = Me, R″ = R‴ = OH).—Anthraquinone (50 g.), suspended in dry ether (500 ml.), was added to methylmagnesium iodide [from magnesium (48 g.) and methyl iodide (125 ml.)] in ether (500 ml.), and the mixture was heated under reflux for 1 hr. The product was added to crushed ice (1 kg.) and ammonium chloride (150 g.) to give a white solid which was shaken with 10% aqueous acetic acid (2 × 1 l.). Crystallisation from benzene gave *trans*-9,10-dihydro-9,10-dihydroxy-9,10-dimethylanthracene monohydrate (from which the water could not be removed by azeotropic distillation with benzene) as plates, m. p. 192—193° (Found: C, 74·8; H, 6·8. Calc. for $C_{16}H_{16}O_2{\cdot}H_2O$: C, 74·4; H, 7·0%). Crystallisation of this *trans*-diol from methanol–benzene gave a white solid, m. p. 188°, from which all the methanol could not be removed by azeotropic distillation with benzene (Found: C, 76·7; H, 6·9. Calc. for $C_{16}H_{16}O_2{\cdot}\frac{1}{2}CH_3{\cdot}OH$: C, 77·3; H, 7·1%).

Evaporation of the ethereal mother-liquors of the reaction gave crystals (20·8 g.) which

[9] Chase and Hey, *J.*, 1952, 553.
[10] Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956, p. 228.

recrystallised from methanol–benzene (1 : 1) to give a solid from which any methanol was removed by azeotropic distillation with benzene; thus was obtained *cis*-9,10-dihydro-9,10-dihydroxy-9,10-dimethylanthracene as plates, m. p. and mixed m. p. 189° (Found: C, 79·8; H, 6·7. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). The infrared spectrum in $CHCl_3$ solution was identical with that of the authentic diol.

9,10-*Dihydro*-9,10-*dimethoxy*-9,10-*dimethylanthracene* (I; R = R′ = Me, R″ = R‴ = OMe).—(a) *From* trans-9,10-*dihydro*-9,10-*dihydroxy*-9,10-*dimethylanthracene*. Concentrated hydrochloric acid (0·02 ml.) was added to the *trans*-diol (0·200 g.) in 1 : 1 methanol–benzene (5 ml.) and after ½ hr., the solution was washed with water and evaporated to give a solid; this crystallised from 1 : 1 methanol–benzene (1·5 ml.) to give 9,10-dihydro-9,10-dimethoxy-9,10-dimethylanthracene (0·106 g.) as plates, m. p. 198—199° (Bachmann [3] reported m. p. 197°). (b) *From* cis-9,10-*dihydro*-9,10-*dihydroxy*-9,10-*dimethylanthracene*. The *cis*-diol (0·200 g.) was treated as above and gave 9,10-dimethoxy-9,10-dimethylanthracene (0·177 g.) as plates, m. p. 198—199° alone or mixed with the diether from the *trans*-diol. In later preparations of the diether, the crude ether-soluble and ether-insoluble diol fractions were used, and gave 75—85% of the required product.

cis-9,10-*Dihydro*-9,10-*dimethylanthracene*-9,10-*dicarboxylic Acid* (Id; R = R′ = Me, R″ = R‴ = CO_2H).—9,10-Dihydro-9,10-dimethoxy-9,10-dimethylanthracene (15 g.), sodium shot (15 g.), and glass chips in dry ether (450 ml.) were shaken for 1 week. After 24 hr., the solution had changed from colourless to greenish-yellow and, after further shaking overnight, had become greenish-black. The product was run into a slurry of solid carbon dioxide in dry ether (500 ml.) and left overnight. Water was added and the aqueous layer was acidified and extracted with ethyl acetate to yield crude 9,10-dihydro-9,10-dimethylanthracene-9,10-dicarboxylic acids (14·3 g., 86%) as a light yellow powder (Found: equiv., 146. Calc. for $C_{18}H_{16}O_4$: equiv., 148). In later preparations, the acids were filtered off from the acidified aqueous layer. Crystallisation from dimethylformamide or elution chromatography with methanol on granular gas-absorption charcoal gave *cis*-9,10-dihydro-9,10-dimethylanthracene-9,10-dicarboxylic acid [1] (50—65%), m. p. and mixed m. p. 310—312°.

cis-9,10-*Dihydro*-9,10-*dimethylanthracene*-9,10-*dicarboxylic Anhydride* (II; R = R′ = Me).—*cis*-9,10-Dihydro-9,10-dimethylanthracene-9,10-dicarboxylic acid (5 g.) was heated in acetic anhydride (10 ml.) for 10 min. Evaporation of the solvent to small volume gave the anhydride [6] (2·3 g., 49%) as cubes, m. p. 220—221°.

cis-9,10-*Dihydro*-9,10-*dimethylanthracene*-9,10-*dicarboxylic Acid Morpholide* (Ia; R = R′ = Me, R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$).—The anhydride (2·4 g.) was treated with morpholine as previously described, and gave the *cis*-monomorpholide [7] (3·0 g., 95%), m. p. 290—291°. Treatment with diazomethane in ether gave the morpholide methyl ester [1] (3·1 g., 100%), m. p. 155—157°.

9,10-*Dihydro*-9-*hydroxymethyl*-9,10-*dimethylanthracene* (Ia or b; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = H).—The foregoing ester morpholide (1·3 g.) and an excess of lithium aluminium hydride were heated in ether under reflux for 6 hr. Sufficient water was added to give a white, granular precipitate, which was filtered off and extracted with ether and benzene. The combined organic solutions were extracted with 10% hydrochloric acid, but no basic material was obtained from the aqueous layer. Evaporation of the washed organic layer and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 9,10-*dihydro*-9-*hydroxymethyl*-9,10-*dimethylanthracene* (0·5 g., 63%) as rhombs, m. p. 101—101·5° (Found: C, 85·4; H, 7·4. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%). A solution of the alcohol (0·10 g.) in dry pyridine (10 ml.) containing acetic anhydride (0·5 ml.) was shaken overnight. The product was poured into water (stirring), left for 5 hr. with occasional stirring, and filtered. Crystallisation of the residue (0·10 g.; m. p. 104—105°) from light petroleum (b. p. 60—80°) gave the *acetate* as needles, m. p. 105—106° (Found: C, 80·6; H, 6·9. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%).

cis-9,10-*Dihydro*-9,10-*dimethylanthracene*-9,10-*dicarboxylic Acid Dimethylamide* (Ia; R = R′ = Me, R″ = CO_2H, R‴ = $CO{\cdot}NMe_2$).—The powdered anhydride (2·7 g.) was dissolved in 20% aqueous dimethylamine (20 ml.). Slow acidification with concentrated hydrochloric acid precipitated a solid (2·9 g.), m. p. 285°, which crystallised from dibutyl ether to give the *acid dimethylamide* as cubes, m. p. 288—289° (Found: C, 74·1; H, 6·5; N, 4·5%; equiv., 323. $C_{20}H_{21}NO_3$ requires C, 74·3; H, 6·6; N, 4·3%; equiv., 323). Treatment with diazomethane in alcohol–ether and crystallisation from ethanol gave the *methyl ester amide* (2·4 g., 88%) as

XUM

rhombs, m. p. 222—223° (Found: C, 75·1; H, 7·1; N, 3·9. $C_{21}H_{23}NO_3$ requires C, 74·8; H, 6·9; N, 4·2%).

Reduction (with Lithium Aluminium Hydride) of the Foregoing Ester Dimethylamide.—The *cis*-ester amide (2·4 g.) and an excess of lithium aluminium hydride were heated in dry ether for 6 hr. Sufficient water was added to give a white, granular precipitate which was filtered off and washed with ether; the combined ether solutions were extracted with 10% hydrochloric acid. The aqueous solutions were made alkaline with 10% sodium hydroxide solution and extracted with ether to give impure *cis*-10-dimethylaminomethyl-9,10-dihydro-9 hydroxymethyl-9,10-dimethylanthracene (0·13 g.) as needles, m. p. and mixed m. p. 115° (Found: equiv., 305. Calc. for $C_{20}H_{25}NO$: equiv., 295).

Evaporation of the acid-washed ether solution, fractional crystallisation of the residue from light petroleum (b. p. 60—80°), and hand-picking of the crystals gave 9,10-dihydro-9-hydroxymethyl-9,10-dimethylanthracene, m. p. and mixed m. p. 100°, and a compound which was thought to be 9,10-*endo*methyleneoxy-9,10-dihydro-9,10-dimethylanthracene, as tufts of colourless blades, m. p. 128—129° (Found: C, 85·9; H, 6·6. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

cis-9,10-*Dihydro*-9,10-*dimethylanthracene*-9,10-*dicarboxylic Acid Monoamide* (Ia; R = R′ = Me, R″ = CO_2Me, R‴ = $CO{\cdot}NH_2$).—The powdered anhydride (1·8 g.) was dissolved in 10% aqueous ammonia (50 ml.) and acidified with concentrated hydrochloric acid to give a white solid (1·9 g.), m. p. 268—269°. Crystallisation of this from 2-methoxyethanol gave the *monoamide* having the above m. p. (Found: C, 73·3; H, 6·0; N, 4·8. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8; N, 4·7%). Treatment with diazomethane in ether gave the *methyl ester amide* as needles (from ethanol), m. p. 240—241° (Found: C, 73·5; H, 6·1; N, 4·5. $C_{19}H_{19}NO_3$ requires C, 73·8; H, 6·2; N, 4·5%).

cis-9-*Aminomethyl*-9,10-*dihydro*-10-*hydroxymethyl*-9,10-*dimethylanthracene* (Ia; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = $CH_2{\cdot}NH_2$).—The ester amide (1·2 g.) and an excess of lithium aluminium hydride were heated in ether for 6 hr. and the product (A) precipitated on treatment with water was extracted as before. Evaporation of the ether gave only a trace of solid. The combined aqueous extracts were made alkaline with 10% sodium hydroxide solution and extracted with ether, which removed a white crystalline material (B) (0·11 g.), m. p. 213°. The precipitate (A) was extracted with chloroform; evaporation of this extract gave a solid (0·72 g.), m. p. 220°, which, crystallised from benzene, gave the cis-*amino-alcohol* as rosettes, m. p. 221° (Found: C, 80·9; H, 8·1; N, 4·9. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9; N, 5·2%), identical with material (B).

cis-9-*Dimethylaminomethyl*-9,10-*dihydro*-10-*hydroxymethyl*-9,10-*dimethylanthracene* (Ia; R = R′ = Me, R″ = $CH_2{\cdot}OH$, R‴ = $CH_2{\cdot}NMe_2$).—The preceding amino-alcohol (0·87 g.) was heated with 90% formic acid (0·7 ml.) and 40% aqueous formaldehyde (0·6 ml.) for 20 hr. Excess of 10% sodium hydroxide solution was added and the resultant precipitate (0·95 g.; m. p. 117°) recrystallised from light petroleum (b. p. 60—80°)–benzene to give the cis-*dimethylamino-alcohol* (0·8 g., 83%) as blades, m. p. 119° (Found: C, 80·8; H, 8·3; N, 4·9%; equiv., 295. $C_{20}H_{25}NO$ requires C, 81·3; H, 8·5; N, 4·7%; equiv., 295).

When this base (1·2 g.) and excess of lithium aluminium hydride were heated together in ether for 6 hr. 92% (1·1 g.) of the base was recovered.

The amino-alcohol (0·4 g.) and acetic anhydride (0·2 ml.) in pyridine (5 ml.) overnight gave the O-*acetate* (0·32 g., 70%) as needles (from hexane), m. p. 62—63° (Found: C, 78·4; H, 8·0; N, 4·1. $C_{22}H_{27}NO_2$ requires C, 78·3; H, 8·1; N, 4·2%).

9,10-*Dihydro*-9-*methylanthracene*-cis-9,10-*dicarboxylic Acid* (Ia; R = Me, R′ = H, R″ = R‴ = CO_2H).—Powdered 9,10-dihydro-9-methylanthracene-9,10-*cis*-dicarboxylic anhydride (1·0 g.) was rapidly dissolved in boiling 10% sodium hydroxide solution (10 ml.), and the solution immediately cooled and acidified with concentrated hydrochloric acid. This precipitated a solid (1·0 g.), m. p. 258—260° (re-solidified and melted at 294—297°), which crystallised from glacial acetic acid to give the cis-*diacid* as rhombs, m. p. 262° (re-solidified and melted at 293°) (Found: C, 72·2; H, 5·0%; equiv., 141. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%; equiv., 141).

9,10-*Dihydro*-9-*methylanthracene*-trans-9,10-*dicarboxylic Acid* (Ib; R = Me, R′ = H, R″ = R‴ = CO_2H).—The 9-methyl-*cis*-dicarboxylic anhydride (0·5 g.) was heated with 10% sodium hydroxide solution (5 ml.) for 3 hr. Then acidification as above precipitated a white solid, the trans-*diacid* (0·51 g.), m. p. 308—309° (from acetic acid) (Found: C, 72·4; H, 4·8%; equiv.,

XUM

140). When the anhydride was heated with the alkali for ½ hr., a mixture of the *cis*- and the *trans*-acid was obtained.

Treatment of the *cis*-diacid (0·2 g.) with diazomethane in ether gave the cis-*dimethyl ester*, plates (from ether–methanol), m. p. 160° (Found: C, 73·8; H, 5·9. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%). The *trans*-acid (0·5 g.) with diazomethane gave the trans-*dimethyl ester*, blades, m. p. 163—165° (from ether) (Found: C, 73·1; H, 5·8%). The m. p. of a mixture of the *cis*- and the *trans*-dimethyl ester was lower than that of either isomer.

When the *cis*- and *trans*-dicarboxylic acids (0·8 g.) were heated severally with acetic anhydride (2·0 ml.) for 6 min. and cooled, 0·54 g. (67%; m. p. 219°) and 0·26 g. (32%; m. p. 212°) respectively of the *cis*-anhydride crystallised.

cis-9,10-*Dihydroanthracene*-10-*carboxymonomorpholide*-9,10-*dicarboxylic Acid* (Ia; R = R′ = H, R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$).—Powdered *cis*-9,10-dihydroanthracene-9,10-dicarboxylic anhydride [6] (1·0 g.) was dissolved in cold 10% aqueous morpholine (50 ml.), and the solution immediately acidified with concentrated hydrochloric acid. This precipitated the acid morpholide (1·3 g., 96%), m. p. 261° alone or mixed with the authentic *cis*-acid morpholide [1] (Found: equiv., 338. Calc. for $C_{20}H_{19}NO_4$: equiv., 337).

cis-9,10-*Dihydro*-9-*methyl*-10-*morpholinocarbonylanthracene*-9-*carboxylic Acid* (Ia; R = Me, R′ = H, R″ = CO_2H, R‴ = $CO{\cdot}NC_4H_8O$).—Powdered 9,10-dihydro-9-methylanthracene-9,10-dicarboxylic anhydride (5·0 g.) was dissolved in 10% aqueous morpholine. Acidification as above precipitated the cis-9-*methyl*-9-*acid* 10-*morpholide* (6·35 g.), needles, m. p. 250—251° (from acetic acid) (Found: C, 71·3; H, 6·0; N, 3·9. $C_{21}H_{21}NO_4$ requires C, 71·8; H, 6·0; N, 4·0%). The *methyl ester morpholide* was prepared by use of ethereal diazomethane and crystallised from ether as cubes, m. p. 148—149° (Found: C, 72·0; H, 6·2; N, 3·8. $C_{22}H_{23}NO_4$ requires C, 72·3; H, 6·3; N, 3·8%).

cis-9,10-*Dihydro*-9-*hydroxymethyl*-9-*methyl*-10-*morpholinomethylanthracene Hydrobromide* (Ia; R = Me, R′ = H, R″ = $CH_2{\cdot}OH$, R‴ = $CH_2{\cdot}NC_4H_8O$,HBr).—The preceding ester morpholide (4·8 g.) was reduced as above. The aqueous extracts were combined, made alkaline with 50% potassium hydroxide solution, and extracted with ether and chloroform. Evaporation of the combined organic layers gave a viscous yellow oil (3·24 g.), a portion of which (0·5 g.) was dissolved in boiling methanolic hydrogen bromide, cooled, and treated with ether. A resulting precipitate (0·46 g.) crystallised from butan-1-ol–ether to give the required *morpholinomethyl hydrobromide* (0·43 g., 52%), as needles which decomposed on being heated (Found: C, 62·4; H, 6·7; N, 3·5%; equiv., 401. $C_{21}H_{26}BrNO_2$ requires C, 62·4; H, 6·5; N, 3·5%; equiv., 404).

cis-9,10-*Dihydro*-10-*methoxycarbonyl*-9-*methylanthracene*-9-*carboxylic Acid* (Ia; R = Me, R′ = H, R″ = CO_2H, R‴ = CO_2Me).—Powdered 9,10-dihydro-9-methylanthracene-9,10-dicarboxylic anhydride (0·3 g.) was dissolved in boiling dry methanol (3 ml.) containing concentrated hydrochloric acid (1 drop). Evaporation of the solvent left the 10-*methyl ester* (0·30 g.). Crystallisation from benzene–light petroleum (b. p. 80—100°) and then from benzene gave plates (0·20 g., 59%), m. p. 150—152° (Found: C, 73·0; H, 5·4. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

Methyl cis-9,10-*Dihydro*-10-*methyl*-10-*morpholinocarbonylanthracene*-9-*carboxylate* (Ia; R = Me, R′ = H, R″ = $CO{\cdot}NC_4H_8O$, R‴ = CO_2Me).—The preceding ester (3·36 g.) was rapidly heated to the b. p. with purified thionyl chloride (5 ml.), then immediately cooled and evaporated under reduced pressure. The residue was dissolved in dry ether (300 ml.) and treated with morpholine (3 ml.), which immediately gave a white solid. Crystallisation from light petroleum (b. p. 80—100°) gave the *ester morpholide* (3·2 g., 79%), as prisms, m. p. 120—121° (Found: C, 72·3; H, 6·4; N, 4·0. $C_{22}H_{23}NO_4$ requires C, 72·3; H, 6·3; N, 3·8%).

cis-9,10-*Dihydro*-10-*hydroxymethyl*-9-*methyl*-9-*morpholinomethylanthracene* (Ia; R = Me, R′ = H, R″ = $CH_2{\cdot}NC_4H_8O$, R‴ = $CH_2{\cdot}OH$).—The last-mentioned morpholide ester (3·0 g.) was reduced and worked up as usual, except that the combined aqueous extracts were made alkaline with 20% sodium hydroxide solution and extracted with ether. Evaporation of the ether gave a yellow solid (1·6 g.) which, crystallised successively from benzene–light petroleum (b. p. 40—60°), benzene–ether, and benzene, gave the *amino-alcohol* (0·8 g., 30%) as colourless rods, m. p. 128—128·5° (Found: C, 77·7; H, 7·8; N, 4·4. $C_{21}H_{25}NO$ requires C, 78·0; H, 7·8; N, 4·3%).

This amino-alcohol (0·2 g.) was shaken overnight in dry pyridine (5 ml.) containing acetic anhydride (0·1 ml.), thus affording its *acetate* (0·16 g., 71%) as lozenges, m. p. 92—93° [from

benzene–light petroleum (b. p. 60—80°)] (Found: C, 75·6; H, 7·5; N, 3·8. $C_{23}H_{27}O_3N$ requires C, 75·6; H, 7·5; N, 3·8%).

The authors thank Dr. G. O. Jolliffe for kindly supplying the authentic *cis*-9,10-dihydro-9,10-dihydroxy-9,10-dimethylanthracene.

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119. *Transition-metal Complexes of Seven-membered Ring Systems. Part III.*[1] *Cycloheptatrieneiron Carbonyl and Related Compounds.*

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The products from the reaction of iron pentacarbonyl and cycloheptatriene have been investigated chemically and by high-resolution nuclear magnetic resonance and infrared spectroscopy. The main products have been shown to be cycloheptatrieneiron tricarbonyl and cyclohepta-1,3-dieneiron tricarbonyl. The nuclear magnetic resonance spectra of cyclohexa-1,3-dieneiron tricarbonyl and bicyclo[4,2,0]octa-2,4-dieneiron tricarbonyl are also interpreted.

IN Part I [2] we described the cycloheptatriene complexes of Group VI transition metals such as $C_7H_8Mo(CO)_3$. In these complexes the metal atom can be considered to attain a formal inert-gas configuration by use of π-electrons from all three double bonds of cycloheptatriene. A similar situation could hold for the seven-membered ring in the azuleneiron carbonyl complexes.[1] By analogy, a compound $C_7H_8Fe(CO)_2$ might have been expected to be obtained by reaction of cycloheptatriene with iron carbonyl.

The interaction of cycloheptatriene and iron carbonyl produces three organometallic complexes in yields which depend on the reaction conditions. If a mixture of the olefin and carbonyl is maintained at 110° ± 5° for about seven days and the unchanged materials are removed under a vacuum at room temperature, fractional distillation of the oily residue gives an orange-yellow liquid (A), $C_7H_8Fe(CO)_2$, n_D^{20} 1·6277, b. p. 70°/0·4 mm. If the reactants are maintained at 135—140° for about seven days and the products separated as before, an orange-yellow liquid (B), n_D^{20} 1·6184, of approximately the same boiling point (74°/0·4 mm.) as (A) is obtained. In this case there is a residue, which after crystallisation from ether gives yellow crystals whose analysis and molecular weight agree with those for a trinuclear complex, $C_{23}H_{16}Fe_3O_9$.

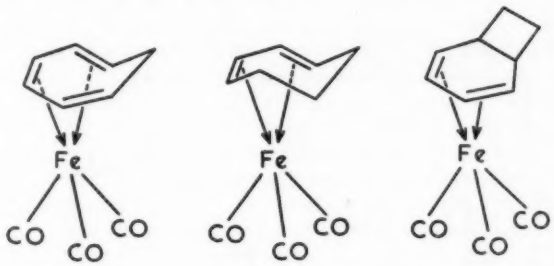
Cycloheptatrieneiron Tricarbonyl.—On the basis of analysis, the substance (A) was originally thought [3] to be cycloheptatrieneiron dicarbonyl; recently, Manuel and Stone [4] have provided preparative details and analytical data for such a dicarbonyl compound, $C_7H_8Fe(CO)_2$. However, this so-called dicarbonyl shows three strong bands in the carbonyl stretching region of its infrared spectrum, at 2050, 1989, and 1975 cm.$^{-1}$, and such a spectrum is inconsistent with a simple dicarbonyl for which only two carbonyl stretching frequencies can be expected. Very careful chromatography of this compound on an alumina column gives as major product a compound analysing as a tricarbonyl, $C_7H_8Fe(CO)_3$, m. p. *ca.* 5°. The infrared and nuclear magnetic resonance spectra of this compound, as discussed below, are also consistent with the structure (I), in which an $-Fe(CO)_3$ group is bound to two adjacent double bonds of the triene, while the third double bond remains unco-ordinated.

[1] Part II, Burton, Pratt, and Wilkinson, *J.*, 1960, 4290.
[2] Part I, Abel, Bennett, Burton, and Wilkinson, *J.*, 1958, 4559.
[3] Burton, Green, Abel, and Wilkinson, *Chem. and Ind.*, 1958, 1592.
[4] Manuel and Stone, *J. Amer. Chem. Soc.*, 1960, **82**, 366.

XUM

Although no experimental details have been given for its preparation, the infrared spectrum of a tropyliumiron dicarbonyl tetrafluoroborate has been given [5] and again three carbonyl stretching frequencies are observed. If this product was prepared from the compound we now know to be a tricarbonyl, by the method used to prepare $[C_7H_7Mo(CO)_3]BF_4$,[6] a reformulation of the iron complex cation as a tricarbonyl species, as its infrared spectrum indicates, will be necessary (see below and IV).

Cyclohepta-1,3-dieneiron Tricarbonyl.—Infrared and nuclear magnetic resonance measurements suggested that the liquid product (B) was a mixture of cycloheptatrieneiron tricarbonyl and some other closely similar compound or compounds. Vapour-phase chromatography indeed showed the presence of two closely related components in the mixture. Careful liquid-phase chromatography on alumina allowed satisfactory separations to be obtained. The more strongly absorbed component was shown by nuclear magnetic resonance measurements to be cycloheptatrieneiron tricarbonyl. Analysis of the less strongly absorbed component gave a stoicheiometry $C_7H_{10}Fe(CO)_3$. The product, m. p. 23°, although similar to the triene complex, showed differences in both the infrared and the nuclear magnetic resonance spectrum. The latter indicated the presence of four olefinic and six aliphatic protons in the molecule, and was consistent with the other evidence in favour of the formulation cyclohepta-1,3-dieneiron tricarbonyl (II). This compound must be formed by hydrogen transfer to the co-ordinated triene system from excess of the triene under the reaction conditions. Confirmation of the nature of the compound was obtained by direct synthesis from cycloheptadiene and iron pentacarbonyl and also by catalytic reduction of $C_7H_8Fe(CO)_3$ (see below).



(I) (II) (III)

Spectroscopic Measurements.—In order to assist in the assignments of lines in the infrared and particularly the high-resolution nuclear magnetic resonance spectra of $C_7H_8Fe(CO)_3$ and $C_7H_{10}Fe(CO)_3$ some closely related compounds, which have a conjugated diene system bound to iron, were also examined. The compound obtained from cyclo-octatriene and iron pentacarbonyl [7] has been conclusively shown by its nuclear magnetic resonance spectrum to be bicyclo[4,2,0]octa-2,4-dieneiron tricarbonyl (III) in agreement with the suggestion made on the basis of indirect evidence.[4] Cyclohexa-1,3-dieneiron tricarbonyl [8] has also been studied and the nuclear magnetic resonance spectrum [9] of butadieneiron tricarbonyl re-measured at 56·4 Mc./sec.

The infrared spectrum of $C_7H_8Fe(CO)_3$ shows a band of medium intensity at *ca.* 1660 cm.$^{-1}$. No bands are found in the 1800—1500 cm.$^{-1}$ region for $C_7H_{10}Fe(CO)_3$ or the iron carbonyl derivatives of cyclohexa-1,3-diene or bicyclo-octadiene. It therefore seems reasonable to assign the 1660 cm.$^{-1}$ band to the C=C frequency of the non-co-ordinated double bond

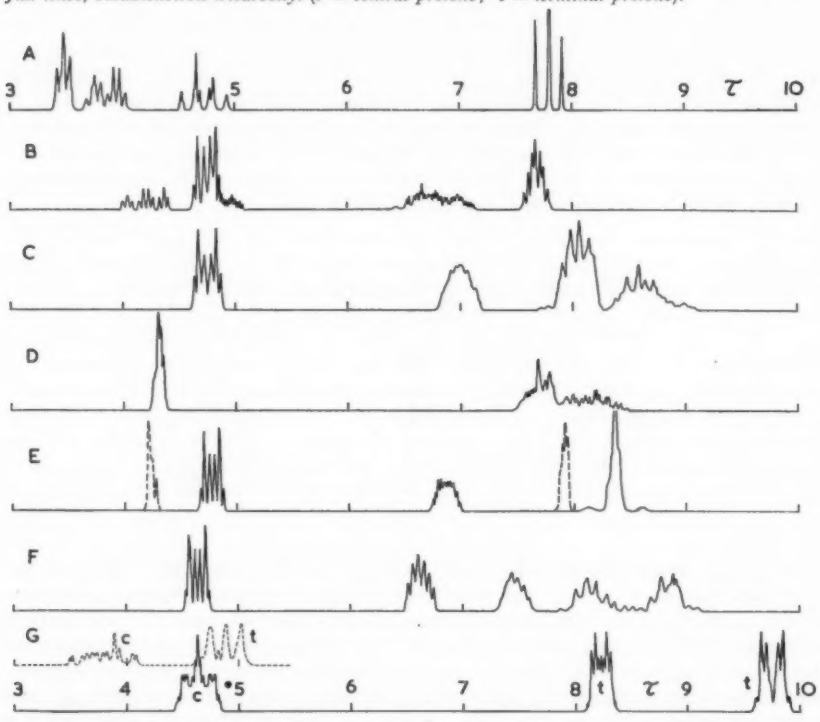
[5] Fischer, *Chem. Ber.*, 1960, **93**, 165.
[6] Dauben and Honnen, *J. Amer. Chem. Soc.*, 1958, **80**, 5570.
[7] Fischer, Palm, and Fritz, *Chem. Ber.*, 1959, **92**, 2645.
[8] Hallam and Pauson, *J.*, 1958, 642.
[9] Green, Pratt, and Wilkinson, *J.*, 1959, 3753; *J.*, 1960, 989.

of the cycloheptatriene ring. The carbonyl stretching region for all the mononuclear iron carbonyl–olefin complexes is very similar, three bands being found under high resolution.

The high-resolution nuclear magnetic resonance spectra are shown in the Figure, and details of the spectra and assignments are given in the experimental section. Chemical shifts are expressed as τ values.*

All four iron compounds show two bands which are attributed to the four protons of the conjugated diene group bound to the iron atom, in addition to the lines in the region 7·5—9·0, which are assigned to aliphatic protons. In contrast to their positions in the

Proton resonance spectra of iron tricarbonyl derivatives of olefins at 56·45 Mc/sec. *Magnetic field increases from left to right.* A, *Cycloheptatriene.* B, *Cycloheptatrieneiron tricarbonyl.* C, *Cyclohepta-1,3-dieneiron tricarbonyl.* D, *Cyclohepta-1,3-diene.* E, *Broken lines, cyclohexa-1,3-diene; full lines, cyclohexa-1,3-dieneiron tricarbonyl.* F, *Bicyclo[4,2,0]octa-2,4-dieneiron tricarbonyl.* G, *broken lines, butadiene; full lines, butadieneiron tricarbonyl* (*c* = *central protons*; t = *terminal protons*).



olefins themselves, where the olefinic proton resonances lie at low fields, one of the co-ordinated " olefinic " bands occurs at high fields (7·0—6·5) and the other remains at low fields. A similar separation of the co-ordinated olefinic resonances into high- and low-field groups has been previously found for other conjugated olefin–metal complexes,[1,9] and it was shown that the low-field band arises from the " central " protons of the diene grouping while the high-field band arises from the " terminal " protons. The spectra of the present iron tricarbonyl complexes show that a similar assignment is valid for them also. The centre of the low-field band occurs at exactly the same position, 4·76, for $C_7H_8Fe(CO)_3$ and $C_7H_{10}Fe(CO)_3$ and is very close to this position in the hexadiene and

* $\tau = 10{\cdot}00 - x$, where x is the line position in p.p.m. on the low-field side relative to tetramethylsilane as internal reference.

bicyclo-octadiene compounds. The symmetrical fine structure is the same at 40 and 56·4 Mc./sec. and is produced by the electron-coupled spin–spin interaction among the four diene protons. The coupling constants can be evaluated by standard methods [10] if these protons are treated as an A_2X_2 group, an approximation which is adequate when considering the " central " protons. The coupling between the " terminal " positions is very small or zero; the coupling of one " central " proton with the other " central " proton is ~4·8 c./sec., with the adjacent " terminal " proton is 6·6—7·6 and with the distant terminal proton is 1·2—1·6 c./sec. These values are consistent with the proposed structures.

The position of the high-field band changes from one compound to another more than does that of the low-field band, probably because the " terminal " protons are more affected by the different groups attached to the co-ordinated conjugated diene system. The structure of the high-field band should be similar to that of the low-field band, but it is made complicated by the additional coupling of the " terminal " protons of the diene grouping with the adjacent aliphatic [and in $C_7H_8Fe(CO)_3$, cycloalkene] protons.

In the bicyclo-octadiene complex, the resultant structure is fairly simple, since there is only one (tertiary) proton adjacent to each " terminal " proton, producing mainly an additional doublet splitting. In the cyclohexa-1,3-diene complex and in $C_7H_{10}Fe(CO)_3$, the additional splitting will be in the form of triplets due to the adjacent $>CH_2$ groups and the resultant structure could not be resolved. In $C_7H_{10}Fe(CO)_3$, the width of this band is independent of the measuring frequency, suggesting that the " terminal " protons of the diene grouping are equivalent, as would be expected. The corresponding band in $C_7H_8Fe(CO)_3$ is wider and its width decreases with the measuring frequency, indicating a chemical shift of *ca.* 0·2 p.p.m. between the two non-equivalent " terminal " protons. This again would be expected on the basis of structure (I) since one of these " terminal " protons is adjacent to a $>CH_2$ group and the other to an olefinic group. These two groups will also produce different additional splittings on the " terminal " protons and although the band in $C_7H_8Fe(CO)_3$ shows considerable fine structure it is not easy to interpret it.

The remaining bands at *ca.* 8·05 and 8·6 p.p.m. in the spectrum of $C_7H_{10}Fe(CO)_3$ can be assigned to the two $>CH_2$ groups severally; these bands are similar to those of the aliphatic protons in the parent olefin. The $>CH_2$ group in $C_7H_8Fe(CO)_3$ gives rise to the band at 7·7 p.p.m. The overall width of this band decreases slightly with frequency, indicating that the two methylene protons are not equivalent, possibly because one of them is closer to the metal atom. Consequently the $>CH_2$ protons will split each other into doublets. In addition they will each experience doublet splittings from the adjacent " terminal " proton, and from each proton of the unco-ordinated olefin group. Since the band is slightly unsymmetrical, the total splitting of one $>CH_2$ proton is not identical with that of the other.

The protons of the unco-ordinated double bond in $C_7H_8Fe(CO)_3$ are not equivalent, one of them (Ha), which is probably adjacent to the diene group, giving the band at *ca.* 4·25 p.p.m. The other (Hb) gives a band at *ca.* 4·85 p.p.m. which is mostly hidden by the low-field band. Comparison of the spectra at 40 and 56·4 Mc./sec. shows that all of the structure of Ha is due to coupling. Ha and Hb each split the other into a doublet (10·6 c./sec.) and since the splitting is of the same order of magnitude as the shift between them (*ca.* 0·6 p.p.m.), the inner component of each doublet is more intense than the outer. Each component of Ha is then split into a doublet (7·7 c./sec.) by the " terminal " proton and each of the resulting four components is split further into a triplet (2·2 c./sec.) by the two protons of the $>CH_2$ group. The two inner triplets overlap partially to give the appearance of a quartet. Hb must also experience a doublet splitting by the " terminal " proton, and a triplet splitting (1·2 c./sec.), possibly by the $>CH_2$ group, can be observed on two of the unobscured components at 5·0 p.p.m.

[10] Pople, Schneider, and Bernstein, " High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York, 1959, p. 140.

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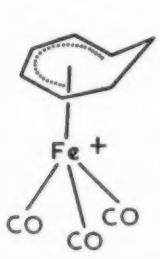
Hence the nuclear magnetic resonance data can be interpreted satisfactorily on the basis of structure (I) and (II) for $C_7H_8Fe(CO)_3$ and $C_7H_{10}Fe(CO)_3$, respectively.

As mentioned previously in the discussion on the structures of the other olefin complexes,[1,9] the shift of the " terminal " protons to a higher field (almost in the aliphatic region of the spectrum) could be consistent with a structure involving σ-bonds from the " terminal " carbon atoms to the metal atom. However, an investigation of the infrared spectra [9] of the complexes did not support such a structure. An up-field shift of olefin-proton resonances is also found in the nuclear magnetic resonance spectrum of cyclo-heptatrienemolybdenum tricarbonyl,[11] whose structure, which has been determined by *X*-ray analysis,[12] again does not appear to have σ-bonds to the metal atom. Hence the latter two methods of structure determination support the π-bonded structures for the metal–olefin complexes and these methods are sufficiently well established to provide more reliable criteria of bond type than is nuclear magnetic resonance of organometallic compounds at the present time.

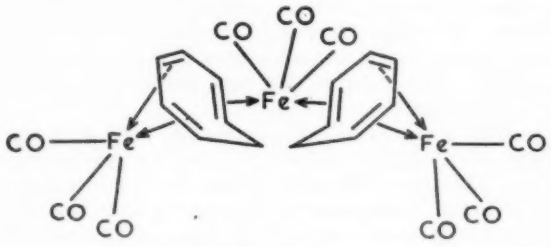
The shifts of the co-ordinated conjugated diene protons can, in fact, be explained on the basis of the π-bonded structure if allowance is made for the long-range shielding contribution to the shift which arises from the anisotropic magnetic polarisation of electrons in the metal–olefin bonds.[11]

Structural Isomerism in Cycloheptatrieneiron Tricarbonyl Complexes.—Compounds possessing a structure similar to that of $C_7H_8Fe(CO)_3$ derived from unsymmetrically substituted cycloheptatrienes can in principle exist as two geometrical isomers, each of these having optically active forms as would be expected for $C_7H_8Fe(CO)_3$ itself. The situation is analogous to that found for the azuleneiron carbonyls.[1] So far, attempts to prepare such isomeric compounds by using methyl thujate have been unsuccessful because of the extensive polymerisation of this triene in the reaction with iron carbonyl. It may be noted, however, that two isomeric forms of cycloheptatrienoneiron tricarbonyl have been reported.[13]

Some Chemical Reactions of Cycloheptatrieneiron Tricarbonyl.—The above evidence clearly shows that in $C_7H_8Fe(CO)_3$ one of the double bonds is not co-ordinated to the metal atom. Attempts have been made to determine whether the compound retains any chemical properties of a normal olefin. In general, the reactions typical of the carbon–carbon double bond do not take place with $C_7H_8Fe(CO)_3$.



(IV)



(V)

Oxidation of the compound with osmium tetroxide, a reaction which gives 1,2-diols from normal olefins, causes immediate decomposition of the iron complex. Oxidation by perphthalic acid, normally giving an epoxide, likewise produces immediate decomposition. It has been suggested that the $-Cr(CO)_3$ group in the arenechromium tricarbonyls has

[11] Bennett, Pratt, and Wilkinson, unpublished work.
[12] Dunitz and Pauling, *Helv. Chim. Acta*, 1960, **43**, 2188.
[13] Hübel and Weiss, *Chem. and Ind.*, 1959, 703.

an electron-withdrawing power on the ring system.[14] The possibility that the $-Fe(CO)_3$ group in $C_7H_8Fe(CO)_3$ might also have a similar effect on the cycloheptatriene ring, with subsequent deactivation of the unco-ordinated double bond towards the normal electrophilic reagents, was taken into account, but reactions with nucleophilic reagents were also unsuccessful. For example, treatment of $C_7H_8Fe(CO)_3$ with either phenyl-lithium or phenylmagnesium bromide under a variety of conditions gave none of the expected products. An attempt to brominate the $>CH_2$ group, using *N*-bromosuccinimide, also caused extensive decomposition.

Although treatment with zinc and acetic or hydrochloric acid caused no apparent change, the high-pressure reduction of $C_7H_8Fe(CO)_3$ has been more rewarding. Reduction in the presence of Raney nickel and hydrogen at 130°/100 atm. caused complete decomposition, and cycloheptane was obtained in high yield. Reduction at room temperature for 24 hours gave a 20% yield of cycloheptadieneiron tricarbonyl.

Halogens react rapidly with $C_7H_8Fe(CO)_3$ but the reactions have not yet been studied in detail. Dry hydrogen chloride and hydrogen bromide are absorbed by the compound in inert solvents, and yellow precipitates obtained. The latter are soluble in water to give yellow solutions which quite rapidly decompose with evolution of carbon monoxide; the solutions give precipitates with large anions such as silicotung-state, Reineckate, etc. The cation has been isolated as yellow crystals of the tetrachloroferrate, stable in air as the solid, and as a hygroscopic bromide. The addition of halogen acid across the unco-ordinated double bond in $C_7H_8Fe(CO)_3$ could be expected to lead to a cation $C_7H_9Fe(CO)_3^+$. The analyses and diamagnetism of the bromide are in accord with this stoicheiometry, and the bromide shows three strong carbonyl stretching frequencies, at 2119, 2061, 1986 $cm.^{-1}$.

Since it has been shown [15] that cyclohexa-1,3-diene can give rise to a π-cyclohexadienylmanganese tricarbonyl, $C_6H_7Mn(CO)_3$, where the C_6H_7 radical is iso-π-electronic with the cyclopentadienyl radical, other cyclic 1,3-dienes can be expected to behave similarly. In the present case the ion, which we now formulate as π-cycloheptadienyliron tricarbonyl, π-$C_7H_9Fe(CO)_3^+$ (IV) is thus similar to the neutral manganese compound.

The Trinuclear Iron Complex.—In view of the structure of $C_7H_8Fe(CO)_3$, it seems reasonable to assign to the trinuclear complex $C_{23}H_{16}Fe_3O_9$ the structure (V), in which an $-Fe(CO)_3$ group is bound to two adjacent double bonds of the cycloheptatriene rings and the two units are bridged by a third $-Fe(CO)_3$ group bound to the remaining double bond of each triene ring. An analogous complex has been obtained by reaction of bi(cycloheptatrienyl) with iron pentacarbonyl, and the polynuclear azuleneiron carbonyl [1] may also be similarly constituted.

Evidence in support of the ability of the unco-ordinated double bond in $C_7H_8Fe(CO)_3$ to be co-ordinated to another metal atom is provided by the reaction of the compound with a concentrated aqueous solution of silver nitrate. A pale yellow, insoluble adduct is obtained but this decomposes quite quickly, the silver ion being reduced to metallic silver, so that analysis could not be undertaken.

Experimental

Microanalyses and molecular weights by the Microanalytical Laboratory, Imperial College.

Interaction of Iron Pentacarbonyl and Cycloheptatriene.—Method (*a*). The olefin (20 g.) and carbonyl (30 ml.) were kept at 110° for 7 days. The unchanged reactants were then removed at 20°/0·4 mm. and an orange-yellow liquid (A) (24 g.), b. p. 70°/0·4 mm., n_D^{20} 1·6277, distilled from the residue. Chromatography of this material in light petroleum on an alumina column gave *cycloheptatrieneiron tricarbonyl*, m. p. *ca.* 5° (Found: C, 52·1; H, 3·9; O, 20·7%; *M*, 230. $C_{10}H_8O_3Fe$ requires C, 51·7; H, 3·5; O, 20·7%; *M*, 232), as an orange-yellow liquid which decomposes in air on prolonged storage.

[14] Nicholls and Whiting, *J.*, 1959, 551.
[15] Winkhaus and Wilkinson, *Proc. Chem. Soc.*, 1960, 311.

Method (*b*). Cycloheptatriene (20 g.) and iron pentacarbonyl (30 ml.) were heated together at 135—140° for 7 days. The unchanged reactants were removed at 20°/0·4 mm. and an orange-yellow liquid (B) (11 g.), b. p. 74°/0·4 mm., n_D^{20} 1·6184, was distilled from the residue. Chromatography in light petroleum on an alumina column gave approximately equal quantities of two complexes. The first complex eluted was *cyclohepta*-1,3-*dieneiron tricarbonyl*, m. p. 23° (Found: C, 51·6; H, 4·4; O, 20·4%; *M*, 230. $C_{10}H_{10}O_3Fe$ requires C, 51·3; H, 4·3; O, 20·5%; *M*, 234), and the second, cycloheptatrieneiron tricarbonyl. The residue remaining after the distillation of compound (B) was washed with light petroleum (3 × 100 c.c.) and crystallisation from ether of the remaining solid gave *di*(*cycloheptatriene*)*tri*(*iron tricarbonyl*) (Found: C, 46·5; H, 2·87; O, 23·5%; *M*, 666. $C_{23}H_{16}O_9Fe_3$ requires C, 45·7; H, 2·65; O, 23·8%; *M*, 604) as yellow crystals.

Other Preparations.—Cyclohexa-1,3-dieneiron tricarbonyl and "cyclo-octatriene"iron tricarbonyl were made by published methods [7,8] and purified by chromatography on alumina.

Reduction of $C_7H_8Fe(CO)_3$ *at Room Temperature.*—A mixture of the compound (3·7 g.) and Raney nickel (0·5 g.) in ethanol (20 ml.) was continuously agitated for 24 hr. under 100 atmospheres of hydrogen. The contents of the autoclave were washed out with ethanol. After filtration, the ethanolic solution was diluted with water, and the aqueous mixture extracted with light petroleum (3 × 50 c.c.). The petroleum extracts were dried ($MgSO_4$) and the solvent was removed at 20°/14 mm. Chromatography of the residual liquid in light petroleum on an alumina column gave $C_7H_{10}Fe(CO)_3$, m. p. 23° (0·74 g., 20%), confirmed by its nuclear magnetic resonance spectrum.

Reduction of $C_7H_8Fe(CO)_3$ *at Elevated Temperature.*—A mixture of the compound (5·5 g.) and Raney nickel (0·5 g.) in ethanol was continuously agitated for 24 hr. at 130° under 100 atmospheres of hydrogen. The contents of the autoclave were washed out with ethanol and after filtration the ethanolic solution was diluted with water. The aqueous mixture was extracted with light petroleum (2 × 50 ml.), and the combined extracts were dried ($MgSO_4$). The solvent was removed and distillation of the residual liquid gave cycloheptane (1·0 g., 40%), n_D^{20} 1·4439, confirmed by its nuclear magnetic resonance spectrum.

The Reaction of $C_7H_8Fe(CO)_3$ *with Hydrogen Chloride and Bromide.*—$C_7H_8Fe(CO)_3$ (3·6 g.) in ethanol (20 ml.), chloroform (20 ml.), and concentrated hydrochloric acid (20 ml.) was left for 6 days in air. Addition of excess of chloroform to the yellow solution produced yellow crystals which were removed and washed with alcohol and ether (0·7 g.) {Found: C, 27·9; H, 2·4; O, 13·5; Fe, 25·4; Cl^-, 32·8. $[C_7H_8Fe(CO)_3][FeCl_4]$ requires C, 27·9; H, 2·1; O, 11·2; Fe, 26·1; Cl^-, 33·1%}. The crystals are readily soluble in water and from a 6N-hydrochloric acid solution the tetrachloroferric acid can be extracted with ether, leaving a pale yellow rather unstable cation in solution. The isolation of the tetrachloroferrate must arise from partial decomposition of the $C_7H_8Fe(CO)_3$ under the reaction conditions. To $C_7H_8Fe(CO)_3$ in light petroleum was added dropwise a solution of hydrogen bromide in light petroleum. The yellow precipitate was centrifuged and washed with light petroleum and dried in a stream of nitrogen; the dry solid is very hygroscopic.

Reduction of the Bromide Salt.—The bromide (*ca.* 2 g.) was dissolved in ethanol (20 ml.), and sodium borohydride added to the solution in small portions. After 15 min. the mixture was diluted with water and extracted with light petroleum. After drying ($MgSO_4$), the solvent was removed and the residual brown oil chromatographed. Cycloheptadieneiron tricarbonyl (0·1 g.) was obtained and its nature confirmed by nuclear magnetic resonance and infrared spectra.

Dipole Moment.—The dipole moment of $C_7H_8Fe(CO)_3$ was measured in a manner similar to that described [1] for the azuleneiron carbonyl. We obtained a value $\mu = 2{\cdot}43 \pm 0{\cdot}04$ D.

Infrared Spectra.—Spectra were taken on a Perkin-Elmer model 21 spectrophotometer with sodium chloride and calcium fluoride optics. Details of the spectra in thin films of the pure liquid are as follows ($cm.^{-1}$):

$C_7H_8Fe(CO)_3$: 3026s, 2992m, 2921w, 2872m, 2841m, 2796m, 2050vs, 1989vs, 1975vs, 1668m, 1665m, 1471m, 1446m, 1419s, 1404s, 1356m, 1346m, 1214s, 1189m, 1153w, 1000m, 943m, 933m, 893m, 864w, 834s, 804m, 704s.

$C_7H_{10}Fe(CO)_3$: 3026m, 2975s, 2918s, 2875s, 2840s, 2046vs, 1977vs, 1458s, 1447s, 1442s, 1404s, 1372m, 1348s, 1338s, 1262w, 1225w, 1194w, 1163m, 1090m, 1060s, 958m, 933w, 868s, 860s, 843m, 803w, 790m.

$C_6H_8Fe(CO)_3$: 3044w, 3004m, 2928s, 2904s, 2884s, 2844s, 2050vs, 1976vs, 1469s, 1454w,

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1432m, 1429w, 1403m, 1337s, 1318w, 1267m, 1237w, 1179s, 1142w, 1118w, 1072m, 1028m, 1008m, 937m, 877m, 862m, 844m, 799w, 641m.

High-resolution Nuclear Magnetic Resonance Spectra.—These were recorded at 22° ± 1° at frequencies of 56·45 and 40 Mc./sec. with Varian Associates spectrometers V4311 and 4310C, respectively. The samples were in 5-mm. (outside diameter) Pyrex spinning tubes, usually in solution in CCl_4. A little tetramethylsilane was added as an internal reference. Line positions were determined by the conventional side-band technique, using a Muirhead–Wigan D695A low-frequency oscillator. Data for each line are presented in the following order: centre position of line in τ values; relative intensity; splitting in c./sec.; assignment and source of observed splitting. The data at 40 and 56·4 Mc./sec. were in full agreement, and in all cases the values of the splittings are the same at the two frequencies.

Cycloheptatriene. (CH_2 group = position 1.) 3·49, two identical protons, H_4 and H_5, structure complex but appears as a " triplet " (3·1 c./sec. between components); 3·91, centre (calculated for A of an AB pair) of two identical protons, H_3 and H_6, each split into a doublet (9·0 c./sec.) by H_2 and H_7, respectively, each component split into a triplet (3·1 c./sec.) by H_4 and H_5; 4·73, centre (calculated for B of an AB pair) of two identical protons, H_2 and H_7, each split into a doublet (9·0 c./sec.) by H_3 and H_6, respectively, each component split into a triplet (6·7 c./sec.) by the CH_2 group, the two triplets overlap to give the appearance of a quartet under moderate resolution; 7·806, two identical protons, CH_2 group, split into a triplet (6·7 ± 0·1 c./sec.) by H_2 and H_7.

Cycloheptatrieneiron tricarbonyl. (Numbering of positions as for cycloheptatriene itself with the iron atom bonded to the diene group 4, 5, 6, 7, so that non-bonded olefin group is 2 and 3.) 4·845, centre (calculated for A of an AB pair) of one proton, H_3, split by H_2 into an unsymmetrical doublet (10·6 c./sec.) of which the components centred at 331·3 c./sec. (on the low-field side of tetramethylsilane at 56·45 Mc./sec.) are less intense than those at 320·7 c./sec., each component split further into a doublet (7·6 c./sec.) by H_4 and into a triplet (2·2 c./sec.) by the CH_2 group, of the four triplets; the inner two overlap to give the appearance of a quartet; 4·76, two identical protons, H_5 and H_6, the " central " diene protons, approximate analysis for these as one half of an A_2X_2 group gives values for the splitting of each proton by the other (4·74 c./sec.), by the nearest of H_4 or H_7 (7·7 c./sec.) and by the furthest of H_7 or H_4 (1·5 c./sec.); about 4·87, centre of H_2 (calculated for B of an AB pair), split into a doublet (10·6 c./sec.) by H_3, components centred at 293·4 c./sec. (the more intense) and 282·3 c./sec., each with further fine structure, including (probably) triplets (3·8 c./sec.) by the CH_2 group; about 6·70, H_4 split into doublet by H_2, H_3, H_5, and H_6, but the fine structure is complex being partly obscured by H_7; about 7·04, H_7 split into triplet by CH_2 group and doublets by H_5 and H_6, fine structure complex and overlapped by H_4; about 7·73 and 7·62, two protons, not identical, CH_2 group, split into doublets by H_3 (2·2 c./sec.) and also by H_2 and H_7.

Cyclohepta-1,3-diene. 4·31, four olefinic protons, almost identical, structure unresolved but unsymmetrical; about 7·69, four protons, two CH_2 groups next to the olefinic groups, complex structure; about 8·08, two protons, central CH_2 group.

Cyclohepta-1,3-dieneiron tricarbonyl. 4·76, two identical protons, " central " diene protons, splittings calculated for A_2X_2 group, each split by the other (4·75 c./sec.) by the nearest " terminal " proton (7·6 c./sec.) and by the furthest " terminal " proton (1·2 c./sec.); 6·99, two identical " terminal " diene protons, each split by the " central " protons (7·6 and 1·2 c./sec.) and into triplets by adjacent CH_2 group, total structure unresolved; about 8·05, four protons, two identical CH_2 groups next to diene group, split by " terminal " proton into doublets and by central CH_2 group into triplets; about 8·55, two protons, central CH_2 group, split by other two CH_2 groups.

Cyclohexa-1,3-diene. 4·22, four olefinic protons, very nearly equivalent, slight unsymmetrical splitting (about 2 c./sec.) by aliphatic groups; 7·92, four aliphatic protons, very nearly equivalent, slight unsymmetrical splitting (about 4 c./sec.) by olefinic protons.

Cyclohexa-1,3-dieneiron tricarbonyl. 4·775, two identical " central " diene protons, splittings calculated (for A_2X_2 group), giving each split by other (4·1 c./sec) and by nearest (6·6 c./sec.) and farthest (1·5 c./sec.) " terminal " protons; 6·86, " terminal " protons, identical or nearly so, each split by " central " diene protons and also into a triplet by the adjacent CH_2 group although structure is not resolved; 8·37, four protons of CH_2 groups, structure not resolved.

Bicyclo[4,2,0]octa-2,4-dieneiron tricarbonyl. 4·64, two identical " central " diene protons, on A_2X_2 assumption each is split by the other (4·8 c./sec.) and by the nearest (6·8 c./sec.) and

furthest (1·6 c./sec.) " terminal " diene protons; 6·63, two " terminal " protons, identical or nearly so, each split by " central " diene protons and also into a doublet by the adjacent tertiary proton; 7·45, two tertiary protons; 8·16 and 8·83, four CH_2 protons, possibly each an AB pair giving an A_2B_2 group, *i.e.*, the two protons of each CH_2 group may not be identical.

The data for butadiene and butadieneiron tricarbonyl have been recorded previously at 40 Mc./sec.;[9] the spectrum of the latter compound at 56·4 Mc./sec. is very similar to that at 40 Mc./sec. apart from the difference in chemical shifts.

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120. *Some Diolefincobalt Carbonyl Complexes.*

By G. WINKHAUS and G. WILKINSON.

Binuclear olefin-substituted cobalt carbonyl complexes of the type $Co_2(CO)_6$(diolefin) and $Co_2(CO)_4$(diolefin)$_2$, in which the bridging carbonyl groups are retained, have been prepared by direct interaction of dicobalt octacarbonyl with norbornadiene, cyclohexa-1,3-diene, and 2,3-dimethylbuta-1,3-diene; the existence of complexes with isoprene and buta-1,3-diene has been shown spectroscopically. Infrared spectra are given and the proton magnetic resonance spectrum of the dimethylbutadiene complex is reported.

OLEFIN-SUBSTITUTED complexes of cobalt carbonyl have been postulated as intermediates in the hydroformylation and other reactions,[1] but relatively few complexes have been isolated. Stable carbonyl compounds have been prepared by direct interaction with tetracyclone [2] and cyclo-octatriene [3] and π-butenyl [4] and π-allyl [5] complexes have been obtained indirectly; π-cyclopentadienylcobalt complexes with cyclopentadienes are also well characterised.[6]

We have now isolated several new binuclear carbonyl complexes (see Table) from the direct interaction of dicobalt octacarbonyl with bicyclo[2,2,1]hepta-2,5-diene (norbornadiene), cyclohexa-1,3-diene, and 2,3-dimethylbuta-1,3-diene. The alkyne-bridged cobalt carbonyl, $Co_2(CO)_6(PhC{\equiv}CPh)$,[7] also reacts with norbornadiene to give the same compound as the octacarbonyl.

Preparations and Properties.—The reactions of the olefins and cobalt carbonyl were carried out in an inert solvent at 40—60° under nitrogen and were completed in 2—4 hr.; higher temperatures and prolonged heating lead to partial decomposition and formation of tetracobalt dodecacarbonyl and metallic cobalt. Both mono- and di-substituted complexes were obtained, and were separated from the reaction products by fractional

$$Co_2(CO)_8 + \text{Diolefin} = Co_2(CO)_6(\text{diolefin}) + 2CO$$
$$Co_2(CO)_8 + 2\text{Diolefin} = Co_2(CO)_4(\text{diolefin})_2 + 4CO$$

extraction and crystallisation and by chromatography on alumina.

[1] See, *e.g.*, Sternberg and Wender, Internat. Conference on Co-ordination Chemistry, London, 1959, *Chem. Soc. Special Publ. No.* 13.
[2] Weiss and Hubel, *J. Inorg. Nuclear Chem.*, 1959, **11**, 42.
[3] Fischer and Palm, *Z. Naturforsch.*, 1959, **14**, b, 508.
[4] Jonassen, Stearns, Kenttämaa, Moore, and Whittaker, *J. Amer. Chem. Soc.*, 1958, **80**, 2586; Aldridge, Jonassen, and Pulkinnen, *Chem. and Ind.*, 1960, 374.
[5] Heck and Breslow, *J. Amer. Chem. Soc.*, 1960, **82**, 750.
[6] Green, Pratt, and Wilkinson, *J.*, 1959, 3753.
[7] Greenfield, Sternberg, Friedel, Wotiz, Markby, and Wender, *J. Amer. Chem. Soc.*, 1956, **78**, 120.

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The disubstituted compounds from norbornadiene and dimethylbutadiene were isolated in good yield, from cyclohexadiene in low yield; in all cases the yield of the monosubstituted compound was very low and for cyclohexadiene the product could not be isolated in a pure state.

Under similar conditions we were unable to obtain evidence for complexes from bicyclo[2,2,2]octa-2,5-diene, cyclo-octatetraene, cyclo-octa-1,5-diene, or *p*-benzoquinone, but when isoprene and butadiene were used spectroscopic evidence for the existence of complexes was obtained though the products could not be obtained in a pure state. Chromatography of the isoprene reaction mixture also yielded a fraction which showed no bridging carbonyl stretching frequencies but has not been fully investigated at present.

The compounds form orange-red needles from ether or light petroleum, apart from the cyclohexadiene complex which crystallises in golden-yellow plates. The solids are stable in air at room temperature but decompose without melting when heated; the disubstituted products are the most stable thermally but even the monosubstituted products are more stable than cobalt carbonyl itself. The compounds cannot be sublimed in a vacuum without extensive decomposition. Whereas the monosubstituted compounds are readily soluble in common organic solvents, the disubstituted ones are fairly soluble only in chloroform, less in benzene and carbon disulphide, and sparingly soluble in ether and petroleum. All solutions are quite air-sensitive, decomposition being particularly rapid in chloroform which decomposes the norbornadiene and cyclohexadiene compounds even in absence of air.

Spectra.—The infrared spectra of the compounds in solution show frequencies characteristic for both terminal and bridging carbon monoxide groups (see Table); these, together with the diamagnetism and analyses of the compounds, show that the carbon

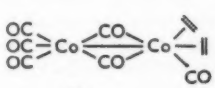
Infrared spectra of the olefin complexes (*in* CCl_4 *and* CS_2 *with* CaF_2 *optics*, 2200—1700 *cm.*$^{-1}$ *region*).

Compound	C–O stretching modes [a] Terminal	Bridging
$Co_2(CO)_6$(norbornadiene)	2083s, 2054m, 2030vs	1840sh, 1820s
$Co_2(CO)_4$(norbornadiene)$_2$	2021vs, 1996ms	1798s
$Co_2(CO)_4$(cyclohexa-1,3-diene)$_2$	2045vs, 2015vs	1809s
$Co_2(CO)_6$(2,3-dimethylbutadiene)	2087s, 2046vs, 2021vs	1850sh, 1830s
$Co_2(CO)_4$(2,3-dimethylbutadiene)$_2$	2005vs, 2025sh	1805s
Isoprene complex [b]	2080m, 2063m, 2040vs	1834s
Butadiene complex [b]	~2050m	~1815m

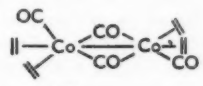
[a] Dicobalt octacarbonyl shows bands at 2070, 2043, 2025, and 1858 cm.$^{-1}$ (Cable, Nyholm, and Sheline, *J. Amer. Chem. Soc.*, 1954, **76**, 3373) but under high resolution further splitting of both terminal and bridging frequencies is observed (Cotton and Monchamp, *J.*, 1960, 1882). [b] Not obtained pure.

monoxide bridging groups in the octacarbonyl are preserved and that the diolefin has replaced two or four of the terminal carbon monoxide groups in the carbonyl.

The monosubstituted complexes (I) show three frequencies characteristic of terminal carbon monoxide groups only slightly shifted compared to the octacarbonyl.



(I)



(II)

In the spectra of the disubstituted compounds (II) (which can in principle have isomers, although no evidence was obtained for them in chromatographic separations), two terminal carbonyl frequencies of unequal intensity are observed; in the dimethylbutadiene complex only one band with a weak shoulder was observed. It is not possible to draw reliable structural conclusions from the spectra in the absence of *X*-ray data, particularly since the

bridge system may be non-planar, as suggested for cobalt octacarbonyl,[8] and other complications such as those observed [9] for the similar molecule $[\pi\text{-}C_5H_5Fe(CO)_2]_2$ which also has two briding carbonyl groups and a carbon monoxide on each metal atom. The spectra in the bridging carbonyl region show one band, but since shoulders were observed in some cases, this band may be more complex under high resolution. The shift to lower wave numbers in the sequence $Co_2(CO)_8$, $Co_2(CO)_6$(diolefin), $Co_2(CO)_4$(diolefin)$_2$ (see Table), may be due to a lowering of strain in the bridge-ring system or to the lower capability of the olefins relative to carbon monoxide to accept π-electron density from the metal atom, which would also be in accordance with the lower terminal carbonyl frequencies in the disubstituted compounds as compared to the octacarbonyl.

The pattern of the remainder of infrared spectra is generally similar to that of the olefins themselves; the stretching frequencies for $>CH_2$ and $>CH$ groups are lowered by 25—60 cm.$^{-1}$ on co-ordination but the C=C stretching frequencies in the free hydrocarbons (1650—1550 cm.$^{-1}$) are not observed in the complexes, being replaced by absorptions in the region 1470—1425 cm.$^{-1}$.

Owing to the low solubility or instability in suitable solvents the proton magnetic resonance spectra could not be obtained except in the case of the disubstituted dimethylbutadiene complex, $Co_2(CO)_4(C_6H_{10})_2$. In chloroform solution the compound shows three lines. The methyl groups give a line at $\tau = 8{\cdot}19$ of width about 1·4 c./sec. The terminal protons give two lines of equal intensity and width (2·4 c./sec.) at $\tau = 7{\cdot}84_5$ and 8·37. In each $=CH_2$ group the protons are probably not equivalent,[6,10] each contributing to one of the observed lines. These lines must have fine structure, since they are broader than the methyl line, but it was not possible to resolve this structure and all the lines appear to be slightly broadened by the presence of small amounts of paramagnetic impurity or decomposition product. In the parent 2,3-dimethylbuta-1,3-diene, the terminal olefinic protons would occur at about $\tau = 5{\cdot}2$, and their shift to higher fields on bonding to the transition metal is similar to that found in other, similar complexes.[6,10]

Experimental

Microanalyses and molecular weights (ebullioscopic in benzene) by the Microanalytical Laboratory, Imperial College.

Infrared spectra were measured on a Perkin–Elmer model 21 spectrometer with both sodium chloride and calcium fluoride optics. High-resolution proton magnetic resonance spectra were taken at 56·5 Mc./sec. on a Varian Associates Model 4300B spectrometer at 22° ± 2° in concentrated solution in chloroform in spinning 5-mm. (outside diameter) tubes; shifts are referred to tetramethylsilane (τ values).

All preparations and most operations were performed in a nitrogen atmosphere.

Reaction of Cobalt Carbonyl with Norbornadiene.—A mixtre of cobalt octacarbonyl (0·86 g., 2·5 mmoles) and norbornadiene (4·6 g., 50 mmoles) in light petroleum (b. p. 40—60°) (30 ml.) was refluxed for 2 hr. Gas was evolved and an orange-red product precipitated. After removal of solvent and exces of olefin at 30°/1 mm., the product, *dinorbornadienedicobalt tetracarbonyl*, was crystallised repeatedly from ether, forming red needles [0·72 g., 70% based on $Co_2(CO)_8$], decomp. 147° (Found: C, 52·0; H, 3·8; O, 15·7; Co, 28·6%; *M*, 424. $C_{15}H_{16}O_4Co_2$ requires C, 52·2; H, 3·9; O, 15·5; Co, 28·5%; *M*, 414). Small quantities of the monosubstituted derivative were also found in the reaction mixture; this compound was obtained in higher yield by using equimolar quantities (2·5 mmoles) of the reagents under conditions similar to the above. After removal of solvent and excess of carbonyl the product was chromatographed on an alumina column using benzene–light petroleum as eluant. The first fraction gave *norbornadienedicobalt hexacarbonyl*, which was crystallised from petroleum at −40° as red needles, decomp. 97° (0·05 g., 5%) (Found: C, 41·2; H, 2·6; O, 25·1%; *M*, 379. $C_{13}H_8O_6Co_2$ requires C, 41·3; H, 2·1; O, 25·4%; *M*, 378). The second fraction gave the disubstituted product (0·3 g.).

[8] Mills and Robinson, *Proc. Chem. Soc.*, 1959, 156.
[9] Cf. Cotton, Stammreich, and Wilkinson, *J. Inorg. Nuclear Chem.*, 1959, **9**, 3.
[10] Cf. Green, Pratt, and Wilkinson, *J.*, 1960, 989.

XUM

Reaction of Cobalt Carbonyl with Cyclohexa-1,3-diene.—A mixture of dicobalt carbonyl (0·86 g.) and cyclohexa-1,3-diene (1·6 g.) in light petroleum (b. p. 60—80°) (40 ml.) was refluxed for 4 hr. After removal of solvent and excess of olefin, the dark residue was extracted with chloroform and chromatographed on alumina with light petroleum–chloroform as eluant. Crystallisation of the eluted product from ether gave golden plates, decomp. >100° (0·06 g., 6%), of *dicyclohexa-1,3-dienedicobalt tetracarbonyl* (Found: C, 49·2; H, 4·8; O, 16·4. $C_{16}H_{16}O_4Co_2$ requires C, 49·3; H, 4·1; O, 16·4%). In the infrared spectrum of the crude reaction mixture, a weak peak at *ca.* 1830 cm.$^{-1}$ was observed, indicating the presence of a small quantity of the monosubstituted compound.

Reaction of Cobalt Carbonyl with 2,3-Dimethylbuta-1,3-diene.—Cobalt carbonyl (0·86 g.) and the olefin (4·1 g.) in light petroleum (40 ml.) were refluxed for 2 hr. After removal of volatile matter, the orange residue was dissolved in ether and chromatographed on alumina with light petroleum–ether (85 : 15) as eluant. The first fraction, after recrystallisation from ether, gave red needles of *di-(2,3-dimethylbuta-1,3-diene)dicobalt tetracarbonyl* (0·6 g., 60%) (Found: C, 48·8; H, 5·3; O, 16·5; Co, 29·9%; *M*, 433. $C_{16}H_{20}O_4Co_2$ requires C, 48·8; H, 5·1; O, 16·2; Co, 29·9%; *M*, 394). The second fraction gave red needles, from light petroleum at −20°, of *2,3-dimethylbuta-1,3-dienedicobalt hexacarbonyl* (0·04 g., 5%) (Found: C, 37·9; H, 3·8; O, 24·8. $C_{12}H_{10}O_6Co_2$ requires C, 39·2; H, 3·7; O, 26·1%).

Reaction of Diphenylacetylenedicobalt Hexacarbonyl with Norbornadiene.—The compound and excess of norbornadiene in light petroleum were refluxed for 2 hr. The red product, on crystallisation from ether, was found to be identical with the disubstituted product from the reaction of cobalt carbonyl and norbornadiene.

Infrared Spectra.—Details of the spectra excluding the carbonyl region (in CCl_4 and CS_2; cm.$^{-1}$) are as follows (the spectra of the disubstituted compounds are incomplete owing to low solubility):

$(C_7H_8)Co_2(CO)_6$: 3008m, 2963m, 2927m, 2850w, 1475w, 1430m, 1310m, 1185m, 1162m, 1087w, 907w, 870w, 720w, 673m, 655s.

$(C_7H_8)_2Co_2(CO)_4$: 3010m, 2960m, 2925m, 2840w, 1425m, 1308m, 1184m, 1156w, 657m.

$(C_6H_8)_2Co_2(CO)_4$: 2980m, 2929w, 2859m, 1460w, 1434m, 1385m, 1353m, 1180m, 806m.

C_6H_{10}: 3082s, 3005sh, 2960s, 2910sh, 2880sh, 1791m, 1707m, 1605s, 1447vs, 1376vs, 1180s, 809vs.

$C_6H_{10}Co_2(CO)_4$: 3060w, 2980s, 2925s, 2860m, 1485s, 1469m, 1462m, 1434m, 1403m, 1382m, 1260m (to 1200 cm.$^{-1}$ only).

$(C_6H_{10})_2Co_2(CO)_4$: 3055m, 2990s, 2920s, 2870sh, 1480s, 1464s, 1453s, 1430s, 1402m, 1382s, 1272w, 1187w, 1029vs, 1005m, 922m, 673m, 635m.

We thank the Ethyl Corporation for financial support (to G. Winkhaus) and Dr. L. Pratt for assistance with nuclear magnetic resonance measurements. Gifts of cobalt carbonyl (Mond Nickel Co. Ltd.), norbornadiene (Shell Chemical Co. Ltd.), and dimethylbutadiene (U.S. Rubber Co.) are gratefully acknowledged.

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XUM

121. *Theoretical Temperature-dependence of the Rate of Isomerization of Cyclopropane.*

By N. B. Slater.

The theoretical temperature-dependence of the first-order rate constant for the isomerization of cyclopropane is estimated for the quantum harmonic oscillator model of unimolecular reactions. The results are in significant disagreement with Falconer, Hunter, and Trotman-Dickenson's experimental results,[1] and a tentative modification of the theoretical formula is suggested.

Concurrently with an accurate determination [2] of the pressure-dependence of the first-order rate constant for the isomerization of cyclopropane to propene, a theoretical calculation was made and was found [3] to give good agreement over the wide range of pressure of the experiments. The calculation was based on the author's " harmonic oscillator " theory of unimolecular reactions and on classical mechanics. Subsequently this theory has been put into a quantum version,[4] which makes little change in the form of the pressure-dependence but departs from the Arrhenius form of temperature-dependence of the high-pressure rate constant. (There is a similar, but less conspicuous, effect when in activated complex theory one passes from classical to quantum partition functions.) The new experiments by Falconer *et al.*[1] give the cyclopropane rate constant at one effectively high pressure over a wide range of temperature, and so are useful for theoretical comparisons. These new experimental results lie much closer to an Arrhenius form than do the theoretical results for the quantum oscillator theory. The purpose of this paper is to explain briefly the theoretical calculations, and to indicate a pragmatic adjustment of the theoretical form which would resolve the discrepancy.

In the quantum oscillator theory, the (high-pressure) first-order rate constant at absolute temperature T is

$$k = \nu \exp(-q^2/2\sigma^2) \text{ sec.}^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where

$$\sigma^2 = \tfrac{1}{4}h \sum_{i=1}^{n} \alpha_i^2 \nu_i \coth(h\nu_i/2kT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

with $\nu_1, \ldots, \nu_n$ the normal vibration frequencies of the molecule, and ν^2 a mean square frequency obtained by dividing the expression (2) into a similar sum with ν_i replaced by ν_i^3. The rate (1) represents the mean probability per second for molecules to dissociate (or isomerize), on the assumption that this requires a particular internal dimension q_1 to reach a critically high value q. The constants α_i arise in the expression $\sum \alpha_i Q_i$ for q_1 as a sum of normal co-ordinates Q_i, which are treated as quantum oscillators of frequencies ν_i; σ^2 is the mean square of this sum for an assembly at temperature T. The limiting form of equation (1) at high temperature is the Arrhenius form $\nu \exp(-E/kT)$ with $E = q^2/\sum \alpha_i^2$; this is also the general classical-mechanical result.

To apply the quantum form of equation (1) to the isomerization of cyclopropane, the reaction co-ordinate or dimension q_1 will be taken to be the diminution (from the equilibrium configuration) of the distance between a carbon and a non-adjacent hydrogen atom; there is, in this case, an extra factor of 12 in equation (1) corresponding to the number of distances of this type in the molecule. The same criterion for isomerization was used in the classical calculations in ref. 3; accordingly the vibrational parameters α_i and frequencies will be taken from Table 4 of that paper, with again $n = 13$ as the effective number of

[1] Falconer, Hunter, and Trotman-Dickenson, following paper.
[2] Pritchard, Sowden, and Trotman-Dickenson, *Proc. Roy. Soc.*, 1953, *A*, **217**, 563.
[3] Slater, *Proc. Roy. Soc.*, 1953, *A*, **218**, 224.
[4] Slater, " Theory of Unimolecular Reactions," Cornell Univ. Press, Ithaca, New York, and Methuen, London, 1959, Chapter X.

independent modes of vibration.* The quantum mean frequency ν may be treated as a constant, as it varies only from $4{\cdot}12 \times 10^{13}$ to $4{\cdot}23 \times 10^{13}$ over the temperature range that will be considered here.

The basic calculation for the present theory is of the sum (2) as a function of temperature. It is convenient to write

$$t = 1000/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and to introduce in equation (2) the function (with $\alpha^2 = \sum \alpha_i^2$)

$$1/\mathrm{f}(t) = \sum(\alpha_i^2/\alpha^2)(\nu_i/10^{13}) \coth (\boldsymbol{h}\nu_i/2\boldsymbol{k}T) \quad . \quad . \quad . \quad . \quad . \quad (4)$$

With the symmetry factor 12, the rate constant (1) is now written

$$k = 12\nu \exp\{-M \,.\, \mathrm{f}(t)\}, \quad M = 2q^2/(10^{13}\boldsymbol{h}\alpha^2) \,. \quad . \quad . \quad . \quad . \quad . \quad (5)$$

To match the range $T = 808$—$693°$ of the experiments, the function (4) was calculated for the range

$$t = 1{\cdot}24\text{—}1{\cdot}44 \quad \text{with} \quad \Delta t = 0{\cdot}02 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

It will be sufficient here to represent these calculations by quoting the extreme and middle entries, namely:

$$\mathrm{f}(1{\cdot}24) = 0{\cdot}233082, \quad \mathrm{f}(1{\cdot}34) = 0{\cdot}244297, \quad \mathrm{f}(1{\cdot}44) = 0{\cdot}254539 \quad . \quad . \quad (7)$$

and also the approximate formula:

$$\mathrm{f}(t) = A + Bt - \tfrac{1}{2}Ct^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where $A = 0{\cdot}013179, \quad B = 0{\cdot}237667, \quad C = 0{\cdot}097300$

This formula represents all the entries with an error under 5×10^{-6}.

The experimental results of Falconer *et al.* were close to the Arrhenius form

$$k_{\mathrm{exp}} = 10^{15{\cdot}3} \exp(-E_{\mathrm{exp}}/\boldsymbol{R}T); \quad E_{\mathrm{exp}} = 65{,}084 \text{ cal. mole}^{-1} \quad . \quad . \quad . \quad (9)$$

To gauge the discrepancy between this and the theoretical form, an estimate is required of the unknown parameter q or M in expression (5). This may be found by considering activation energy, although the choice of M is not unique, so that attention will be concentrated on relative changes of rate with temperature rather than on absolute values. The natural definition of E_a, the activation energy per mole, for a rate constant k is:

$$E_a/\boldsymbol{R} = -\partial \ln k/\partial(1/T) = -1000\partial \ln k/\partial t \quad . \quad . \quad . \quad . \quad . \quad (10)$$

For the experimental form (9), $E_a = E_{\mathrm{exp}}$. For the form (5), with the approximation (8) for f(t), we have:

$$E_a/\boldsymbol{R} = 1000M \,.\, \mathrm{f}'(t) \simeq 1000M(B - Ct) \quad . \quad . \quad . \quad . \quad . \quad (11)$$

From the values of B and C above, this E_a is respectively 9% less and 9% greater at $t = 1{\cdot}44$ and $t = 1{\cdot}24$ than at the middle, $t = 1{\cdot}34$, of the range (6).

To estimate M in expression (5), the temperature-dependent E_a of (11) is to be identified at some temperature with the experimental value in (9). If the middle value $t = 1{\cdot}34$ is chosen in (11), then

$$M = (E_{\mathrm{exp}}/\boldsymbol{R})/\{1000(B - 1{\cdot}34C)\} = 305{\cdot}31 \,. \quad . \quad . \quad . \quad . \quad . \quad (12)$$

This gives for the exponent $M \,.\, \mathrm{f}(t)$ of the theoretical form (5), at $t = 1{\cdot}44$, $1{\cdot}34$, $1{\cdot}24$, respectively,

$$77{\cdot}713, \quad 74{\cdot}586, \quad 71{\cdot}162 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

* Use should be made here of a new calculation of these parameters by A. P. Cox; but the revision is unlikely to affect the high-pressure rate constant, although it might affect lower-pressure rate predictions.

XUM

The corresponding values of E_{exp}/RT from (9) are

$$47{\cdot}167, \quad 43{\cdot}892, \quad 40{\cdot}616 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Comparing these numbers, we see that the increase in $\ln k$ between "temperatures" $t = 1{\cdot}44$ and $1{\cdot}24$ is $6{\cdot}551$ in both (13) and (14), so that the relative increase in k is the same theoretically and experimentally over the total span of the temperature range. On the other hand, the difference between the first two numbers in (13) is $0{\cdot}148$ less than in (14). Thus the theoretical increase in $\log k = 0{\cdot}4343 \ln k$ is $0{\cdot}064$ less than the experimental increase, in passing from the lowest to the "mean" temperature, that is, from $t = 1{\cdot}44$ to $1{\cdot}34$. This indicates that the theoretical plot of $\log k$ against $1/T$ is concave upwards, dipping below the linear experimental plot by an amount $0{\cdot}064$ at the middle of the range. The discussion of Falconer *et al.* indicates that this discrepancy considerably exceeds their experimental error.

If in identifying the activation energies an extreme value $t = 1{\cdot}44$ or $1{\cdot}24$ were used in (12), a similar relative concavity would be found in the theoretical curve, although the values (13) of the theoretical exponent would change by $\pm 9\%$. The values (13) are in all these cases considerably larger than (14). Thus, as the remaining factor $12\nu = 5 \times 10^{14}$ in the theoretical rate constant (5) is similar to the experimental pre-exponential factor in (9), the absolute values of k on the present theory are much too small compared with the experimental values.

An Empirical Modification.—The limiting form of expression (2) as T tends to zero is

$$\sigma_0^2 = \tfrac{1}{4} h \sum \alpha_i^2 \nu_i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

which is seen to be the zero-point mean square of the co-ordinate $q_1 = \sum \alpha_i Q_i$ with all oscillators Q_i in their ground states. It would seem plausible [4] (although not in accord with the spirit of the original formulation of the present quantum model) to exclude all or much of the dispersion σ_0^2 from σ^2 in formulating the rate constant (1). The effect of such a modification may be tested by replacing σ^2 in (1) by $\sigma_1^2 = \sigma^2 - 0{\cdot}756\sigma_0^2$. The rate constant (5) now becomes [with M defined as before in (5)]:

$$k = 12\nu \exp \{-M \,.\, f_1(t)\} \text{ sec.}^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

where $1/f_1(t)$ is the previously tabulated $1/f(t)$ decreased by a carefully chosen constant, which is in fact the source of the coefficient $0{\cdot}756$ in σ_1^2 above. With this choice, it is found that with an error generally under 6×10^{-6}, $f_1(t)$ can be represented as

$$f_1(t) = A' + B't. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

where $A' = -0{\cdot}095056, \quad B' = 0{\cdot}440673$

To this order of accuracy, the amended rate constant (16) is of an Arrhenius form, with activation energy given by $E_a/R = 1000MB'$ (cf. 11). Identifying this with the experimental value in (9) gives

$$M = 74{\cdot}30 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

and for the rate constant (16)

$$k = 12\nu \exp \{-M(A' + B't) = 12\nu \, e^{7{\cdot}065} \exp (-E_{exp}/RT). \quad . \quad . \quad (19)$$

The effective pre-exponential factor is now rather high, although the discrepancy is much less than in the previous calculation.

The effect of excluding zero-point contributions has also been briefly discussed in connection with the application of the present quantum theory to nitryl chloride,[4] for which as for cyclopropane the simple classical theory gives a satisfactory picture. This

XUM

confirms the need for a fresh examination of the theoretical basis, since a correct theory must essentially be quantal; an exactly Arrhenius form of rate constant is not, however, to be expected.

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122. *The Thermal Isomerization of Cyclopropane.*

By W. E. FALCONER, T. F. HUNTER, and A. F. TROTMAN-DICKENSON.

The thermal isomerization of cyclopropane to propene at 30 cm. pressure has been studied by gas-chromatographic analysis between 420° and 535°. The rate constant is given by

$$\log k_{30}\ (\text{sec.}^{-1}) = (15{\cdot}296 \pm 0{\cdot}007) - (65{,}084 \pm 26/2{\cdot}303\boldsymbol{R}T).$$

The Arrhenius equation represents the results within the limits of accuracy of the experiments.

CHAMBERS and KISTIAKOWSKY [1] first reliably determined the temperature-dependence of the isomerization of cyclopropane to propene. They found that their results for this rate constant at 469·6°, 499·5°, and 518·6° were best represented by

$$\log k\ (\text{sec.}^{-1}) = 15{\cdot}17 - (65{,}000/2{\cdot}303\boldsymbol{R}T)$$

They considered that the activation energy had been determined within ±2000 cal. mole^{-1}, but their results cannot readily be analysed statistically because they were rather few and because of the corrections that had to be applied to extrapolate them to infinite pressure. The isomerization of cyclopropane is of theoretical importance because it is one of the few clean unimolecular reactions whose rate constant varies over an experimentally accessible range of pressure. The interpretation of this dependence requires a knowledge of the Arrhenius equation and it was possible that the small divergence between theory and experiment arose because the A factor was not accurately known.[2,3] Slater's theoretical treatment [4] of the reaction based on a model with quantized oscillators predicts that the activation energy of the reaction should vary by 18% between 693° and 808° K. Although this variation seems large, the effect is that the theoretical curve for log k lies only 0·064 unit (16% for k) below the Arrhenius curve if the two curves are made to coincide at the extreme temperatures. The perfect fit of the rates at the extreme temperatures cannot be realised in practice; therefore the effect to be detected is a deviation of +0·032 log unit at the extreme temperatures and −0·032 log unit in the middle. The detection of such small trends calls for unusually self-consistent results.

Chambers and Kistiakowsky analysed the mixtures of propene and cyclopropane formed during the reaction by oxidation of the propene with potassium permanganate. This was cumbersome and accurate to only about ±2%. Pritchard, Sowden, and Trotman-Dickenson [5] later absorbed the propene with a mixture of mercuric acetate and mercuric nitrate. Much smaller samples could be analysed but the accuracy was not much better. Gas-chromatographic separation with a Janak nitrometer detector was used in this work because it is capable of an accuracy of a few parts in a thousand.

The rate constants for 30 cm. pressure are given by the expression

$$\log k_{30}\ (\text{sec.}^{-1}) = (15{\cdot}296 \pm 0{\cdot}007) - (65{,}084 \pm 26/2{\cdot}303\boldsymbol{R}T)$$

[1] Chambers and Kistiakowsky, *J. Amer. Chem. Soc.*, 1934, **56**, 399.
[2] Trotman-Dickenson, "Gas Kinetics," Butterworths, London, 1955.
[3] Slater, *Proc. Roy. Soc.*, 1953, *A*, **218**, 224.
[4] Slater, preceding paper.
[5] Pritchard, Sowden, and Trotman-Dickenson, *Proc. Roy. Soc.*, 1953, *A*, **217**, 563.

XUM

The Table of deviations shows that few of the runs deviated from the Arrhenius expression by as much as 1% (0·004 log unit), and the mean deviation is less. This does not mean that the rate constants are known with that precision because the absolute temperature scale is known with much less certainty than the relative temperatures of the runs. For this reason the uncertainty in the Arrhenius parameters is considerably greater than that computed statistically. Fortunately it is the relative temperature scale that is of primary importance for testing the adequacy of the quantized oscillator model. The model predicts that if the experimental range is roughly divided into three parts with $10^3/T$ equal to 1·237—1·305, 1·305—1·373, and 1·373—1·442, then the mean deviation from the Arrhenius expression for each of the parts should be +0·011, −0·021, and +0·011. The mean deviations found are +0·002 ± 0·0028, −0·0010 ± 0·0019, and 0·0010 ± 0·0031. These figures show that the quantum theory differs from the observations by about five times the experimental error.

A more stringent test would depend either upon more accurate measurement of the rate constant or upon the extension of the temperature range. The accuracy of the measurements is limited by many factors, such as the measurement of the lengths of the runs, the estimation of reaction zone and the dead space, the timing of short runs, and the analysis of the products. Consideration of the probable sizes of the errors involved leads

Deviations of the experimental rate constants from the Arrhenius equation.

Temp. (° K)	10^3 (log $k_{exp.}$ − log $k_{calc.}$)	Temp. (° K)	10^3 (log $k_{exp.}$ − log $k_{calc.}$)	Temp. (° K)	10^3 (log $k_{exp.}$ − log $k_{calc.}$)
808·34°	+2·5	773·48°	+4·3	732·85	−0·6
806·14	−0·6	773·57	−2·6	720·05	+2·0
806·38	−0·8	762·06	+1·8	720·04	+1·9
797·50	+5·5	761·95	−1·8	719·66	+3·9
797·29	+0·3	761·90	−1·8	710·60	−3·9
796·23	−0·9	761·87	−3·1	706·95	+1·0
784·81	−4·3	751·68	+1·7	706·93	+6·0
784·63	−3·2	751·83	−2·1	700·00	−4·1
784·79	−0·6	737·41	−4·0	693·87	−0·3
784·38	+2·2	737·56	−0·7	693·62	+2·0

to an error fully equal to the reproducibility of the runs obtained here. The temperature range cannot be extended downwards because evidence was found that in runs three times as long as the longest recorded in the Table, about 1% of the propene disappeared, presumably by polymerization. Shorter runs require a flow system. Equally accurate relative measurements can be made with flow systems, but there is always some doubt about the continuity of the temperature scale with that of a static apparatus and of the effective reaction volume. These uncertainties cancel the advantages of shortening the reaction time.

The results obtained here can be corrected to infinite pressure with the aid of Slater's classical harmonic oscillator treatment which states that the position of the plot of log k/k_∞ against log p varies with temperature according to the expression

$$\Delta \log p = \tfrac{1}{2}n \log (T_2/T_1)$$

where n is the number of modes of vibration; in this instance $n = 14$. Hence at infinite pressure

$$\log k \text{ (sec.}^{-1}) = 15{\cdot}45 - (65{,}600/2{\cdot}303RT)$$

The result is in excellent agreement with Chambers and Kistiakowsky's [1] and with

$$\log k \text{ (sec.}^{-1}) = 15{\cdot}2 - (65{,}500/2{\cdot}303RT)$$

reported by Rabinovitch, Schlag, and Wiberg [6] after this work was begun. None of the discrepancy between the experimental and theoretical variations of k with pressure can, therefore, be ascribed to errors in the Arrhenius parameters.

[6] Rabinovitch, Schlag, and Wiberg, *J. Chem. Phys.*, 1958, **28**, 504.

The Arrhenius equation is similar to that for the structural isomerization of methylcyclopropane: [7]

$$\log k\ (\text{sec.}^{-1}) = 15{\cdot}45 - (65{,}000/2{\cdot}303RT)$$

and of 1,1-dimethylcyclopropane: [8]

$$\log k\ (\text{sec.}^{-1}) = 15{\cdot}05 - (62{,}600/2{\cdot}303RT)$$

The small changes in the rate constants with substitution are difficult to reconcile with the fission of a C–C bond as the rate-determining step.

Experimental.—Apparatus. The Pyrex reaction vessel (50 c.c.) was immersed in a lead bath placed in an electric furnace. The furnace-temperature was controlled by a Sunvic RT 2 resistance thermometer controller whose sensing element was in a copper tube brazed to a brass sheet which closely fitted the cylindrical former that carried the windings. The reaction temperature was measured by a double base-metal thermocouple in a well in the centre of the reaction vessel. The thermocouple was calibrated against a platinum/platinum–13% rhodium couple.

Materials. Cyclopropane (B.O.C.) was degassed and shown by analysis to contain no impurities.

Procedure. Runs were started by admitting 30 cm. pressure of cyclopropane to the reaction vessel. After a convenient time the mixture was frozen into a trap cooled by liquid oxygen. A few seconds later the trap was connected to the vacuum-line so that small quantities of non-condensable gases should not prevent the freezing-out of larger quantities of C_3 hydrocarbons. The mixture was analysed on a column of 1 ft. of activated alumina, followed by 3 ft. of firebrick with 20% of ethylene glycol saturated with silver nitrate, coupled to a Janak nitrometer detector. The amount of reaction always lay between 25% and 77%. The variation of rate constant with degree of conversion at one temperature was not systematically studied. The early work showed that the isomerization accurately obeys first-order kinetics. Results are in the Table.

We thank Mr. W. A. Gibbons, Miss E. L. Metcalfe, Dr. R. Shaw, and Dr. R. F. Smith who carried out preliminary experiments.

CHEMISTRY DEPARTMENT, EDINBURGH UNIVERSITY. [*Received, July 18th*, 1960.]

[7] Chesick, *J. Amer. Chem. Soc.*, 1960, **82**, 3277.
[8] Flowers and Frey, *J.*, 1959, 3953.

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123. *Optical Studies of 2,2′-Di-t-butylbiphenylcarboxylic Acids and of 2′-t-Butylbiphenyl-2-carboxylic Acid.*

By MARY S. LESSLIE and URSULA J. H. MAYER.

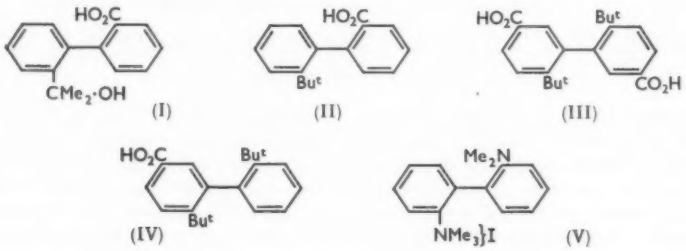
The synthesis of 2′-t-butylbiphenyl-2-carboxylic acid, 2′,6-di-t-butylbiphenyl-3-carboxylic acid and of 6,6′-di-t-butylbiphenyl-3,3′-dicarboxylic acid is described. The strychnine and the brucine salts of the mono-t-butylbiphenyl acid undergo second-order asymmetric transformation in ethanol. The di-t-butylbiphenyl acids have been resolved and show high optical stability.

CORBELLINI and ANGELETTI [1] found that the brucine salt of the 2′-(hydroxyalkyl)biphenyl-2-carboxylic acid (I) underwent second-order asymmetric transformation in ethanol and, later, Jamison and Turner [2] showed that it also underwent first-order transformation in chloroform. We have now prepared 2′-t-butylbiphenyl-2-carboxylic acid (II) and found

[1] Corbellini and Angeletti, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis., mat., nat.*, 1932, **15**, 968.
[2] Jamison and Turner, *J.*, 1942, 437.

XUM

that its strychnine and brucine salts undergo second-order asymmetric transformation; no first-order transformation was observed. On the other hand, 6,6′-di-t-butylbiphenyl-3,3′-dicarboxylic acid (III) and 2′,6-di-t-butylbiphenyl-3-carboxylic acid (IV) were resolved and showed high optical stability.



Scale models based on known atomic radii show that in the di-t-butyl acids the two benzene rings cannot become coplanar since, owing to their volume, the two tertiary butyl groups cannot pass the hydrogens in the 2,2′-positions. Interconversion of the (+)- and (−)-forms is therefore inhibited. This is in marked contrast to the asymmetry of 2′-dimethylamino-2-biphenylyltrimethylammonium iodide (V) which arises from the " dynamic effect " of the less bulky $\cdot NMe_3^+$ group:[3] the active quaternary iodides whilst optically stable in cold aqueous solution had a half-life of 125 minutes at 99·5°.

Methyl 2′-t-butylbiphenyl-2-carboxylate (II) was prepared by heating together equimolecular proportions of methyl *o*-iodobenzoate and *o*-iodo-t-butylbenzene in presence of copper bronze. A mixture of 2,2′-di-t-butylbiphenyl, dimethyl diphenate, and methyl 2′-t-butylbiphenyl-2-carboxylate was obtained. The hydrocarbon was removed by distillation of the mixture under reduced pressure but the esters could not be separated either by distillation or by fractional crystallisation. The mixture of esters was therefore hydrolysed and the acids were eventually separated by tedious and rather wasteful crystallisations from glacial acetic acid (in which the diphenic acid was slightly less soluble) and from aqueous ethanol. *o*-Iodo-t-butyl benzene was prepared in greatly improved yield by modifications of Shoesmith and Mackie's method.[4] 2,4-Dinitro-t-butylbenzene was reduced in aqueous solution with sodium disulphide and the nitro-amine was deaminated through the diazonium fluoroborate or with hypophosphorous acid. The above authors found that during the diazotisation of *o*-amino-t-butylbenzene decomposition of the diazonium sulphate set in at −8° and we therefore performed the diazotisation at −35° and allowed the reaction mixture to warm to −13°, then added it to aqueous potassium iodide solution. This procedure resulted in greatly enhanced yields of the iodo-compound.

The dimethyl ester of the acid (III) was obtained by heating methyl 3-iodo-4-t-butylbenzoate with copper bronze. The preparation of the iodo-ester from methyl 3-amino-4-t-butylbenzoate hydrochloride (or sulphate) presented unexpected difficulty because of the instability of the diazonium salt. The crude iodo-ester was a green viscous oil; it was distilled under reduced pressure and appeared to be homogeneous. Addition of light petroleum produced a wax-like solid; this crystallised from light petroleum and was found to be a 1 : 1 molecular compound of the iodo-ester and methyl 3-hydroxy-4-t-butylbenzoate. The iodo-ester is a liquid at room temperature and was obtained from the mother-liquors after all the molecular compound had been removed. It is surprising that the molecular compound distils under reduced pressure as if it were an individual substance,

[3] Shaw and Turner, *J.*, 1933, 135.
[4] Shoesmith and Mackie, *J.*, 1928, 2334.

XUM

and in ethereal solution it did not yield the phenolic component when extracted with cold alkali. On the other hand, when the solid compound was stirred with cold 30% aqueous sodium hydroxide or warmed with a 10% solution of sodium hydroxide a mixture of the iodo-ester and sodium 3-hydroxy-t-butylbenzoate was obtained. By this means the iodo-ester was recovered from the molecular compound. In later preparations the solid compound was not isolated, but the oil obtained after vacuum-distillation was stirred with successive amounts of cold concentrated sodium hydroxide solution and the sodium salt of the hydroxy-acid was removed by repeated washing with water. The iodo-ester thus obtained was hydrolysed, and the iodo-acid was purified by crystallisation from methanol and from light petroleum, then converted into its methyl ester.

When heated with copper bronze the molecular compound gave 5,5′-dimethoxycarbonyl-2,2′-di-t-butylbiphenyl ether.

Ethyl 3-amino-4-t-butylbenzoate hydrochloride was also prepared. The diazonium chloride derived from it was very unstable but there was no evidence of compound formation between the iodo- and the hydroxy-ester. Washing with alkali failed again to remove the hydroxy-ester from the ethereal solution but on removal of the solvent a mixture of the two solid esters was obtained. These were easily separated by crystallisation from ethanol in which the hydroxy-ester was very soluble.

The methyl ester of the monocarboxylic acid (IV) was prepared by heating equimolecular amounts of methyl 3-iodo-4-t-butylbenzoate and *o*-iodo-t-butylbenzene. The products were partially separated by distillation under reduced pressure, the main fraction consisting of a mixture of 2,2′-di-t-butylbiphenyl and the required unsymmetrical ester. This was hydrolysed with ethanolic potassium ethoxide, and the hydrocarbon removed by extraction with ether. The unsymmetrical acid was then obtained on acidification of the alkaline solution.

The strychnine salt of the monocarboxylic acid (II) was prepared in ethanol, and a series of crops was obtained whose rotations in chloroform solution were approximately the same ($[\alpha]_{5791}$ $-46{\cdot}0° \pm 0{\cdot}4°$). The acid regenerated from these salts was lævorotatory and it was thus apparent that the strychnine salt had undergone second-order asymmetric transformation. Recrystallisation of the salts from methanol was more satisfactory than from ethanol since considerable dissociation into free acid and base occurred in the latter solvent. (When prepared in methanol the strychnine salt also underwent asymmetric transformation.) The purest salt had $[\alpha]_{5791}$ $-49{\cdot}9°$ in chloroform and racemised slowly during several days at room temperature. In boiling ethanol it racemised quickly. The highest rotation obtained for the acid was $[\alpha]_{5791}$ $-24{\cdot}3°$ and $[\alpha]_{5461}$ $-29{\cdot}8°$ in ethanol. Racemisation of the (−)-acid in ethanol was studied at 57°, 67°, and 79° (half-life 35, 14·1, and 5·6 minutes respectively). The activation energy was 24 kcal. mole^{-1}. The brucine salt was also prepared in ethanol and it, too, underwent second-order asymmetric transformation but to a smaller extent. The maximum rotation obtained for the recovered acid was $[\alpha]_{5791}$ $+7{\cdot}7°$ in ethanol.

6,6′-Di-t-butylbiphenyl-3,3′-dicarboxylic acid (III) was resolved through its brucine salt. The (+)-acid salt, which was the more soluble in ethanol, was a gel but it was possible to separate the two salts since their solubilities in ethanol differed considerably.

The free acids were obtained having $[\alpha]_{5791}$ $\pm 18{\cdot}6°$ ($\pm 0{\cdot}3°$) in acetone. The acids showed high optical stability and were not racemised in aqueous alkali or in pyridine at the boiling point.

2′,6-Di-t-butylbiphenyl-3-carboxylic acid (IV) was converted into its strychnine salt, and the two diastereoisomers were separated by crystallisation from ethanol. The (+)-acid salt was crystalline and was readily obtained optically pure whereas the (−)-acid salt was an oil. The (±)-acid, however, was more sparingly soluble than the active acids, and the crude (−)-acid obtained from the oil was isolated optically pure by crystallisation from methanol. The acids had $[\alpha]_{5791}$ $\pm 25{\cdot}5°$ and $[\alpha]_{5461}$ $\pm 28{\cdot}4°$ ($\pm 0{\cdot}5°$) in chloroform. The active acid retained its activity after sublimation at 130°/1 mm. and even after melting.

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Experimental

2,4-*Dinitro-t-butylbenzene*.—t-Butylbenzene (100 g.) was added, with stirring, within ½ hr., to nitric acid (500 c.c.; *d* 1·51) at 0°. Then the solution was left at 60—65° for 15 min. and poured on crushed ice. The crude dinitro-compound was filtered off and was melted under boiling water (3 l.), then cooled quickly with vigorous stirring. After crystallisation from ethanol the dinitro-t-butylbenzene was obtained as white prisms which became yellow on exposure to light and had m. p. 63—64° (yield 85%).

3-*Nitro*-4-*t-butylaniline*.—A hot solution of sodium disulphide (2 mol.) in water (200 c.c.) was added within a few minutes to a vigorously stirred suspension of 2,4-dinitro-t-butylbenzene (45 g.) in boiling water (500 c.c.). After 1 hour's boiling, with stirring (the volume of water being maintained), the mixture was cooled and the crude nitro-amine was filtered off. After purification through its hydrochloride the base was crystallised from ethanol and from light petroleum (b. p. 40—60°). It melted at 55—56° (yield 75%).

o-*Nitro-t-butylbenzene*.—(*a*) 3-Nitro-4-t-butylaniline (60 g.) was diazotised in hydrochloric acid and the diazonium solution kept at 0—10° for 1 hr. (this was essential, otherwise much base was recovered). To the filtered solution hydrogen fluoroborate was added, and the precipitated diazonium fluoroborate was filtered off, washed with ether, and dried *in vacuo* over sulphuric acid (85 g.). It was decomposed by adding it gradually to a boiling mixture of ethanol (3 parts) and concentrated sulphuric acid (½ part). The nitro-t-butylbenzene was obtained with b. p. 102—104°/6 mm. (40 g., 72%).

(*b*) The aniline (60 g.) was diazotised as above and the filtered diazonium solution was added with stirring to hypophosphorous acid (600 c.c.) at 0°. By this method the nitro-t-butylbenzene was obtained in 75% yield.

o-*t-Butylaniline*.—The above nitro-compound (70 g.) was reduced with iron filings and water containing a little acetic acid. The base obtained (88%) had b. p. 93°/5 mm.

o-*Iodo-t-butylbenzene*.—*o*-t-Butylaniline (22 g.) was dissolved in dilute sulphuric acid (*d* 1·2; 120 c.c.) and cooled to −35°. A concentrated aqueous solution of sodium nitrite (10·5 g.) was added within 5 min. and the mixture allowed to warm in the freezing solution (carbon dioxide and ethanol) to −13° during 2 hr. The resultant brown gelatinous suspension was added to an aqueous solution of potassium iodide (75 g.). The diazonium iodide which separated decomposed readily. The mixture was made alkaline and the crude iodo-hydrocarbon from two similar experiments was steam-distilled. The distillate was extracted with ether, and the ethereal extract was washed successively with acid, sodium metabisulphite solution, acid, and water, then dried ($CaCl_2$). After removal of the solvent the residue was distilled and *o*-iodo-t-butylbenzene, b. p. 94—96°/3 mm. (68—78%), was obtained.

2,2′-*Di-t-butylbiphenyl*.—The above iodo-hydrocarbon (20 g.) reacted with copper bronze (20 g.) at 225° (bath). The reaction was complete after ½ hr. and the product was extracted with chlorobenzene. The solvent was removed and the residue distilled under reduced pressure. 2,2′-*Di-t-butylbiphenyl*, b. p. 140°/2 mm., was obtained. Light petroleum (b. p. 60—80°; 2 c.c.) was added to the oil, and the hydrocarbon, which crystallised, separated from ethanol as stout plates, m. p. 63—64° (Found: C, 90·2; H, 9·9. $C_{20}H_{26}$ requires C, 90·2; H, 9·8%).

2′-*t-Butylbiphenyl-2-carboxylic Acid*.—A mixture of *o*-iodo-t-butylbenzene (20 g.) and methyl *o*-iodobenzoate (20 g.) reacted with copper bronze at 210° (bath) for ½ hr. The product was extracted with chlorobenzene and after removal of the solvent the residue was distilled under reduced pressure. The lower fractions collected were liquids; the main fraction, b. p. 160—180°/5 mm. (13 g.), crystallised on addition of light petroleum (b. p. 40—60°) and was recrystallised three times from light petroleum (b. p. 40—60°). It was found to be an inseparable mixture of dimethyl diphenate and methyl 2′-t-butylbiphenyl-2-carboxylate and it was therefore hydrolysed with ethanolic potassium ethoxide. The resultant mixture of acids was separated by fractional crystallisation from glacial acetic acid followed by crystallisation from aqueous ethanol. *2′-t-Butylbiphenyl-2-carboxylic acid* crystallised from aqueous ethanol in needles, m. p. 182—183° (Found: C, 80·1; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%).

3-*Nitro*-4-*t-butylbenzoic Acid*.—*p*-t-Butylbenzoic acid (50 g.) was added gradually to ice-cold nitric acid (500 c.c., *d* 1·51). Then the solution was kept at 60° for 15 min. and poured on ice. The acid crystallised from dilute acetic acid in small prisms, m. p. 162—163° (65%). Decarboxylation of the acid, followed by nitration of the resulting nitro-hydrocarbon, to give

2,4-dinitro-t-butylbenzene, m. p. 63—64° (Shoesmith and Mackie [4]), confirmed that the acid was the 3-nitro-isomer.

Methyl 3-Nitro-4-t-butylbenzoate.—3-Nitro-4-t-butylbenzoic acid (150 g.) was converted into its methyl ester, b. p. 162°/6 mm., plates, m. p. 45—46° (from methanol) (Found: C, 60·8; H, 6·5. Calc. for $C_{12}H_{15}NO_4$: C, 60·7; H, 6·4%). It was described as an oil by Kelbe and Pfeiffer.[5]

The *ethyl ester* had b. p. 162—165°/5 mm., m. p. 22—24° (Found: C, 62·1; H, 6·7. $C_{13}H_{17}NO_4$ requires C, 62·1; H, 6·8%).

Methyl 3-Amino-4-t-butylbenzoate Hydrochloride.—The above methyl nitro-ester (146 g.) was reduced with iron filings, water, and a little acetic acid at 100°. The mixture was extracted with hot methanol, and the filtered extract freed from the bulk of solvent by distillation. The residue was poured into an excess of concentrated hydrochloric acid at 0°. The resulting paste was filtered off and dried at 100° (121 g., 80%). The *hydrochloride* crystallised from alcohol in thin plates, m. p. 198—200° (Found: Cl, 15·0. $C_{12}H_{18}ClNO_2$ requires Cl, 14·6%).

The corresponding ethyl ester hydrochloride was similarly prepared from ethyl 3-nitro-4-t-butylbenzoate. A pure specimen was not obtained since it was too soluble in all the usual solvents. The free *base* was a viscous oil, b. p. 160°/4 mm. (Found: C, 70·6; H, 9·3. $C_{13}H_{19}NO_2$ requires C, 70·6; H, 8·7%). In attempts to crystallise this hydrochloride from dilute hydrochloric acid it was hydrolysed to *3-amino-4-t-butylbenzoic acid hydrochloride* which crystallised in prisms, m. p. 238—239° (Found: C, 57·5; H, 6·8. $C_{11}H_{16}ClNO_2$ requires C, 57·5; H, 6·9%).

3-Iodo-4-t-butylbenzoic Acid.—To the above methyl ester hydrochloride (44 g.) in concentrated hydrochloric acid at −25° the requisite amount of sodium nitrite in aqueous solution was added quickly. The mixture was left for 90 min., initially at −15°, and allowed to warm to −5°, then quickly added to aqueous potassium iodide solution (46 g.). The resultant oil which contained some low-melting solid was extracted with ether, and the ethereal solution was washed repeatedly with alkali, then successively with sodium metabisulphite solution, acid, and water, and dried. After removal of the ether the residue was distilled. The distillate was a green viscous oil, b. p. 164—168°/10 mm., which on addition of light petroleum (b. p. 40—60°) gave a wax-like solid (25·5 g.). It was recrystallised several times from light petroleum and separated as hair-like needles, m. p. 58—59° (Found: C, 54·8; H, 6·1; I, 24·1. $C_{12}H_{15}IO_2$,$C_{12}H_{16}O_2$ requires C, 54·8; H, 5·9; I, 24·1%).

On several occasions when the pure molecular compound was allowed to crystallise very slowly from light petroleum small rod-shaped crystals were deposited. The supernatant solution was then carefully decanted and immediately the hair-like needles of the molecular compound crystallised. The rods were identified as methyl 3-hydroxy-4-t-butylbenzoate.

The diazotisation of the base hydrochloride was repeated many times, the temperature conditions being varied and also the time allowed for the reaction to proceed. From all experiments the molecular compound was obtained in good yield; if the temperature was maintained too low or insufficient time allowed for complete diazotisation then unchanged base was recovered. The diazonium sulphate appeared to be even more unstable than the chloride and when it was added to aqueous potassium iodide the molecular compound was again the main product. The mother-liquors from the crystallisation of the molecular compound were repeatedly concentrated and cooled to −35° until no more solid compound separated. The crude liquid iodo-ester was then obtained on removal of the solvent. The iodo-ester was recovered from the molecular compound by addition of cold 30% aqueous sodium hydroxide solution. After being stirred for a few minutes the hydroxy-ester underwent hydrolysis and was easily removed as the sodium salt of the hydroxy-acid. Under these conditions no hydrolysis of the iodo-ester occurred. Alternatively, the green oil obtained from the vacuum-distillation of the crude " iodo "-product was similarly treated with cold alkali, and the iodo-ester was thus obtained free from the hydroxy-ester. The iodo-ester was hydrolysed with ethanolic potassium ethoxide to *3-iodo-4-t-butylbenzoic acid*, needles, m. p. 202—203° (from ethanol) (Found: C, 43·5; H, 4·4. $C_{11}H_{13}IO_2$ requires C, 43·4; H, 4·3%).

The pure iodo-acid was converted into its *methyl ester*, b. p. 156—158°/4 mm., m. p. ~12° (Found: C, 45·6; H, 4·8. $C_{12}H_{15}IO_2$ requires C, 45·3; H, 4·8%).

The *ethyl ester* crystallised from ethanol in cubes, m. p. 58—59° (Found: C, 47·1; H, 4·9. $C_{13}H_{17}IO_2$ requires C, 47·0; H, 5·2%).

[5] Kelbe and Pfeiffer, *Ber.*, 1886, **19**, 1723.

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Ethyl 3-amino-4-t-butylbenzoate hydrochloride was diazotised under the conditions employed for the methyl ester base. The product was a mixture of the iodo- and hydroxy-esters, each of which was a solid. They were readily separated by crystallisation from ethanol and the less soluble iodo-ester was obtained pure.

Methyl 3-Hydroxy-4-t-butylbenzoate.—Methyl 3-amino-4-t-butylbenzoate hydrochloride (12 g.) was diazotised at −15° and allowed to warm to +10° during which time decomposition with evolution of nitrogen was apparent. When the reaction was complete the solid *ester* which had separated (4·8 g.) was filtered off, dried and crystallised from light petroleum (b. p. 40—60°), forming needles, m. p. 108—109° (Found: C, 69·3; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). Hydrolysis was readily effected by stirring the ester with cold 10% aqueous sodium hydroxide. The sodium salt separated and dissolved to a clear solution when water was added. Acidification gave *3-hydroxy-4-t-butylbenzoic acid*, rectangular needles (from aqueous ethanol), m. p. 187—188° (Found: C, 68·0; H, 7·25. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·25%).

5,5′-Dimethoxycarbonyl-2,2′-di-t-butylbiphenyl Ether.—The molecular compound (methyl 3-iodo-4-t-butylbenzoate, plus methyl 3-hydroxy-4-t-butylbenzoate) (45 g.) reacted with copper bronze at 240° (bath). The product was extracted with chlorobenzene and after removal of the solvent a crystalline *ether* was obtained (4·2 g.) that recrystallised from methanol as rhombohedra, m. p. 173—174° (Found: C, 72·3; H, 7·7; O, 19·3. $C_{24}H_{30}O_5$ requires C, 72·4; H, 7·6; O, 20·1%).

6,6′-Di-t-butylbiphenyl-3,3′-dicarboxylic Acid.—The above iodo-ester (18 g.) reacted vigorously with copper bronze at 235° (bath). The product was extracted with chlorobenzene and after removal of the solvent the crude ester crystallised and was washed with light petroleum (b. p. 40—60°). Two crystallisations from methanol gave *dimethyl 6,6′-di-t-butylbiphenyl-3,3′-dicarboxylate* as needles, m. p. 201—202° (5·5 g., 62%) (Found: C, 75·2; H, 8·0. $C_{24}H_{30}O_4$ requires C, 75·3; H, 7·9%). Ethyl 3-iodo-4-t-butylbenzoate with copper bronze at 245° similarly gave *diethyl 6,6′-di-t-butylbiphenyl-3,3′-dicarboxylate*, needles (from ethanol), m. p. 144—145° (Found: C, 76·0; H, 8·4. $C_{26}H_{34}O_4$ requires C, 76·1; H, 8·4%). Hydrolysis with ethanolic potassium ethoxide of each ester gave *6,6′-di-t-butylbiphenyl-3,3′-dicarboxylic acid*, hexagonal prisms (from acetic acid), m. p. 345° (Kofler block) (Found: C, 74·4; H, 7·5. $C_{22}H_{26}O_4$ requires C, 74·5; H, 7·4%).

2′,6-Di-t-butylbiphenyl-3-carboxylic Acid.—A mixture of methyl 3-iodo-4-t-butylbenzoate (32 g.) and *o*-iodo-t-butylbenzene (26 g.) was heated with copper bronze in a bath at 220°. Then the mixture was extracted with chlorobenzene and after removal of the solvent an oil was obtained. On addition of methanol the symmetrical ester crystallised and was filtered off. The residue was distilled under reduced pressure and the main fraction (7 g.) was collected at 156—180°/2 mm. It was hydrolysed with ethanolic potassium ethoxide and 2,2′-di-t-butylbiphenyl was removed from the alkaline solution by extraction with ether. The acid was then precipitated on acidification of the alkaline solution. *2′,6-Di-t-butylbiphenyl-3-carboxylic acid* crystallised from methanol in slender prisms, m. p. 233° with slight previous softening (Found: C, 81·1; H, 8·5. $C_{21}H_{26}O_2$ requires C, 81·2; H, 8·4%).

Alkaloid Salts of 2′-t-Butylbiphenyl-2-carboxylic Acid.—Rotations of salts were measured at room temperature for " AnalaR " chloroform solutions ($c \sim 1$) and of acid for ethanol solutions ($c \sim 1$) in 2 dm. tubes.

Strychnine salt. To a boiling solution of (±)-acid (5 g.) in ethanol (100 c.c.) strychnine (6·6 g.) was added. The salt which separated overnight at room temperature (8·0 g.) had $[\alpha]_{5791}$ −45·6°. Evaporation of the mother-liquor gavé successive crops whose specific rotations were approximately the same as above. A portion of salt on decomposition gave an acid, $[\alpha]_{5791}$ −19·9°. When prepared in more concentrated solutions of ethanol the specific rotations of the salts were lower and acids were recovered whose specific rotations varied from $[\alpha]_{5791}$ −13·5° to −18·2°. Recrystallising the salt from ethanol gave erratic results because of dissociation into free acid and base; methanol was therefore preferred and recrystallisation from this solvent was continued until the specific rotation of the salt remained constant.

Strychnine (−)-2′-t-butylbiphenyl-2-carboxylate crystallised from methanol in sheaves of rectangular prisms, m. p. 208—212°, $[\alpha]_{5791}$ −49·9°, $[\alpha]_{5461}$ −58·6° (Found: C, 77·3; H, 6·8. $C_{17}H_{16}O_2,C_{21}H_{22}N_2O_2$ requires C, 77·5; H, 6·8%). When it was boiled under reflux in chloroform solution for 15 min. its specific rotation fell to $[\alpha]_{5791}$ −38·2° and $[\alpha]_{5461}$ −44·8°. This salt, the " partial racemate," was always recovered from rotation solutions when the chloroform

was removed by heat or by slow evaporation. When the methanol mother-liquor from recrystallisations was allowed to evaporate slowly to dryness at room temperature the residual salt yielded acid of low rotation ($[\alpha]_{5791}$ −6·3°). All salts were decomposed in the usual manner with ice-cold sodium hydroxide solution. Addition of ice-cold acid to the alkaline solution (after extraction with chloroform) gave the free acid. The purest strychnine salt gave acid, m. p. 185—187°, $[\alpha]_{5791}$ −24·3°, $[\alpha]_{5461}$ −29·8°. Crystallisation from ethanol caused complete racemisation of the acid.

Brucine salt. The (±)-acid (1 g.) and brucine (1·44 g.) were dissolved in boiling ethanol (14 c.c.). After 2 days at 4° the first crop of salt separated (1·2 g.), having $[\alpha]_{5791}$ −23·9° and $[\alpha]_{5461}$ −29·7°. From the reduced mother-liquor a second crop separated with the same rotation. After recrystallisation from ethanol the rotation was unchanged. The acid recovered from the salt had $[\alpha]_{5791}$ +7·7°. The preparation of brucine salt was repeated twice, the rotation of the recovered acids being +3·3° and +5·1°.

Racemisation of (−)-acid. The rate of racemisation in boiling ethanol was measured for a solution (20 c.c.) containing 0·2268 g. of (−)-acid. The temperature was rapidly raised to the b. p. (79°) and after a suitable interval the solution was rapidly cooled to room temperature. Polarimetric readings were taken at 20°. The heating and cooling processes were repeated until racemisation was complete; α_{5791} ($l = 2$) fell from −0·39° to 0°. From a logarithmic plot, k was found to be 0·00207 sec.$^{-1}$ and the half-life 5·6 min. The racemisation of the (−)-acid in ethanol was also followed at 57° and 67° in a well-lagged water-jacketed polarimeter tube ($l = 2$) thermostatically controlled. The rate constants were found to be 0·00033 and 0·00082 sec.$^{-1}$, and the half-life periods 35 and 14·1 min. respectively. From these data the activation energy was found to be 24 kcal. mole^{-1}.

Resolution of 6,6′-Di-t-butylbiphenyl-3,3′-dicarboxylic Acid.—All rotations were measured in " AnalaR " acetone at room temperature (c ~0·5) in 2 dm. tubes. The acid (6·5 g.) and brucine (14·4 g.) were dissolved in ethanol (450 c.c.), and the solution kept overnight at +4°. The first fraction of salt (6·1 g.) separated as rosettes of thin rectangular plates and had $[\alpha]_{5791}$ −41·8°, $[\alpha]_{5461}$ −46·8°. The second fraction (1·4 g.) which separated after concentration of the mother-liquor had $[\alpha]_{5791}$ −42·4°, $[\alpha]_{5461}$ −50·2°. Further concentration of the mother-liquor yielded a gel which contained a small amount of crystalline salt and since the gel was very soluble in ethanol it was possible to separate them. The crystalline salt was recrystallised four times from ethanol and was then optically pure.

Brucine (+)-6,6′-di-t-butylbiphenyl-3,3′-dicarboxylate crystallised from ethanol as a hydrate in rosettes of long, thin rectangular plates, m. p. 210° with previous softening, $[\alpha]_{5791}$ −37·8°, $[\alpha]_{5461}$ −43·9° (Found: C, 65·3; H, 7·4. $C_{22}H_{26}O_4,2C_{23}H_{26}N_2O_4,6H_2O$ requires C, 65·3; H, 7·3%). On being heated *in vacuo* at 70° for several hours the salt lost its water of crystallisation and the loss in weight corresponded to $6H_2O$. On exposure to air the anhydrous salt very quickly reverted to the hydrated form. Decomposition of the above salt yielded (+)-acid, and from the gel the (−)-acid was obtained.

(+)-6,6′-Di-t-butylbiphenyl-3,3′-dicarboxylic acid crystallised from ethanol in glistening plates, from glacial acetic acid in sheaves of rectangular rods, and from aqueous acetic acid in plates. From these solvents it always had solvent of crystallisation which was completely removed only by heating the products *in vacuo* at 130° for several hours. From aqueous acetic acid the (+)-acid crystallised with 1 mol. of water of crystallisation, and had m. p. 345° with loss of solvent at 200° (Kofler block), $[\alpha]_{5791}$ +18·1°, $[\alpha]_{5461}$ +23·6° (Found: C, 70·9; H, 7·2. $C_{22}H_{26}O_4,H_2O$ requires C, 70·9; H, 7·6%).

The *anhydrous acid*, m. p. 345°, had $[\alpha]_{5791}$ +18·6°, $[\alpha]_{5461}$ +24·1° (Found: C, 74·7; H, 7·6. $C_{22}H_{26}O_4$ requires C, 74·5; H, 7·4%).

The *(−)-acid* crystallised from glacial acetic acid with 1 mol. of acetic acid of crystallisation; it had m. p. 345° with loss of solvent at 240° (Kofler block), $[\alpha]_{5791}$ −17·7°, $[\alpha]_{5461}$ −22·8° (Found: C, 69·7; H, 7·2. $C_{22}H_{26}O_4,C_2H_4O_2$ requires C, 69·6; H, 7·3%). Heating *in vacuo* at 130° for several hours gave the unsolvated acid, $[\alpha]_{5791}$ −18·9°, $[\alpha]_{5461}$ −24·2°.

After being boiled in sodium hydroxide or in pyridine solution for 3 hr. the active acid was recovered unchanged.

Resolution of 2′,6-Di-t-butylbiphenyl-3-carboxylic Acid.—Rotations of salts and acids were measured at room temperature in " AnalaR " chloroform (c ~1) in 2 dm. tubes unless otherwise stated.

The above acid (3·1 g.) and strychnine (3·4 g.) were dissolved in ethanol (120 c.c.) and kept

XUM

at room temperature overnight. The first crop of salt (1·4 g.) separated as fine needles, $[\alpha]_{5791}$ −8·9°, $[\alpha]_{5461}$ −11·0°. After concentration of the mother-liquor more salt was obtained (1·2 g.) with approximately the same rotation. On further concentration an oil was obtained that did not crystallise. This was decomposed and gave the crude (−)-acid. The crystalline (+)-acid salt was purified by recrystallisation from ethanol.

Strychnine (+)-2′,6-*di-t-butylbiphenyl*-3-*carboxylate* crystallised from ethanol in slender needles, m. p. 160—161°, $[\alpha]_{5791}$ −9·5°, $[\alpha]_{5461}$ −12·6° (Found: C, 74·2; H, 7·8. $C_{21}H_{26}O_2,C_{21}H_{22}N_2O_2,2H_2O$ requires C, 74·1; H, 7·7%). When heated *in vacuo* at 80° the salt lost 2 mols. of water of crystallisation. The free acids were obtained from the strychnine salts by decomposition with formic acid. (+)-2′,6-*Di-t-butylbiphenyl*-3-*carboxylic acid* crystallised from methanol in needles, m. p. 181—185°, $[\alpha]_{5791}$ +25·5°, $[\alpha]_{5461}$ +28·4° (Found: C, 80·8; H, 8·3. $C_{21}H_{26}O_2$ requires C, 81·2; H, 8·4%). In toluene its rotation was $[\alpha]_{5791}$ +45·4°, $[\alpha]_{5461}$ +51·8°.

The crude (−)-acid was crystallised from methanol, and a small amount of (±)-acid separated. This was filtered off and the mother-liquor was concentrated: the (−)-acid crystallised. Recrystallisation from methanol gave the pure (−)-acid, m. p. 181—185°, $[\alpha]_{5791}$ −25·8° and $[\alpha]_{5461}$ −28·3°.

The active acids melted rather indefinitely and it was suspected that they contained solvent of crystallisation since erratic analytical figures for the same sample were obtained on several occasions. The (−)-acid was therefore heated at 130°/1 mm. and sublimed under these conditions. The *acid* so obtained melted at 192—193° and had $[\alpha]_{5791}$ −65·5° and $[\alpha]_{5461}$ −72·4° in toluene (Found: C, 80·9; H, 8·6%). A portion of the pure (−)-acid was melted and allowed to solidify: its specific rotation in toluene was unchanged.

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BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, August 10th*, 1960.]

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124. *Some Reactions of Tributyl- and Triphenyl-stannyl Derivatives of Alkali Metals.*

By D. BLAKE, G. E. COATES, and J. M. TATE.

Tri-n-butylstannyl-lithium reacts with chlorotrimethylsilane and with carbon dioxide as if it contained butyl-lithium in equilibrium with dibutyltin. Triphenylstannylsodium, which can be prepared from sodium–naphthalene and tetraphenyltin, hexaphenyldistannane, or triphenyltin bromide, reacts normally with ethyl bromide and benzyl chloride, but as a reducing agent with benzophenone, benzoyl chloride, oxygen, carbon dioxide, and sulphur dioxide.

ALKALI-METAL derivatives of trialkyl- and triaryl-stannanes (R_3SnM) are readily prepared by well-known reactions in liquid ammonia solution, but their scope as synthetic reagents is limited by the reactivity of the solvent. Solutions or suspensions of these substances in diethyl ether were later prepared from organolithium reagents and organotin(II) compounds, the latter being prepared either separately [1] or from tin(II) chloride: [2]

$$SnCl_2 + 3RLi = R_3SnLi + 2LiCl$$

Wishing eventually to use reagents R_3SnM for the synthesis of compounds containing bonds between tin and other metals, we found it necessary first to investigate some of the already reported reactions of R_3SnM, many of which appeared unexpected and difficult to understand. For example, in their first paper [2] on triphenylstannyl-lithium, Gilman and Rosenberg obtained the following products on reaction with halides: EtI gave Ph_4Sn,

[1] Wittig, Meyer, and Lange, *Annalen*, 1951, **571**, 195.
[2] Gilman and Rosenberg, *J. Amer. Chem. Soc.*, 1952, **74**, 531.

27%, and Ph_3EtSn, 36%; $Ph{\cdot}CH_2Cl$ gave Ph_4Sn, 60%, and $Ph_3Sn{\cdot}CH_2Ph$, 22%; Ph_3SnCl gave Ph_6Sn_2, 53%; and Ph_3SiCl gave $Ph_3Si{\cdot}SnPh_3$, 71%. They also detected no reaction with benzophenone. In their first paper they found that carbonation yielded no benzoic acid, this result being confirmed in their second [3] and third [4] papers in which they reported the isolation of tetraphenyltin (4·7%) and then both this product (24%) and hexaphenyldistannane (Ph_6Sn_2, 16%).

We confirmed the formation of triphenylsilyltriphenyltin from chlorotriphenylsilane, and that of hexaphenyldistannane from triphenyltin halides, but obtained different results in respect of the other reactions.

Trialkylstannyl Derivatives.—Triethylstannyl-lithium [5] and its n-butyl analogue [2] have also been described, but their only reported reactions are those with ethyl and butyl halides forming the tetra-alkyl compound. We did not investigate the reactions of triethylstannyl-lithium formed from ethyl-lithium, $SnCl_2 + 3EtLi = Et_3SnLi + 2LiCl$, since Gilman and Rosenberg [5] found that free ethyl-lithium was present in the reaction mixture (colour test [6] based on halogen exchange with *p*-bromodimethylaniline) when only 2·5 mol. had been added. Consequently the addition of ethyl-lithium to diethyltin is reversible: $Et_2Sn + EtLi \rightleftharpoons Et_3SnLi$. The reagent would not be useful for the preparation of triethylstannyl derivatives of, for example, reactive metal halides, since the ethyl-lithium present would also react—possibly faster than the Et_3SnLi. Since it was stated [2] that the same colour test indicates the absence of free butyl-lithium until just over 3 mol. have been added to tin(II) chloride, the formation of tri-n-butylstannyl-lithium did not appear to be reversible and the use of this reagent seemed to be promising.

We found, however, that reagents which react rapidly with butyl-lithium react with tri-n-butylstannyl-lithium as if it were a mixture of dibutyltin and butyl-lithium. For example, chlorotrimethylsilane gave butyltrimethylsilane, and carbonation gave dibutyltin

$$Bu_3SnLi \rightleftharpoons Bu_2Sn + BuLi$$
$$BuLi + Me_3SiCl \longrightarrow BuMe_3Si$$

and a mixture of valeric acid and dibutyl ketone. We were unable to find any satisfactory synthetic use for tri-n-butylstannyl-lithium.

Reactions of Triphenylstannyl Alkali-metal Derivatives.—Triphenylstannyl-sodium or -lithium was prepared in practically quantitative yield, as judged by recovery of ethyltriphenyltin after subsequent reaction with ethyl bromide, either from triphenyltin bromide and sodium in liquid ammonia (followed by replacement of ammonia by ether or dimethylformamide) or by Gilman and Rosenberg's method [2] using phenyl-lithium and tin(II) chloride. The liquid-ammonia method gave better yields except in those instances in which the reagent subsequently used is sensitive to ammonia. We found that triphenylstannylsodium, prepared in liquid ammonia, tenaciously retains ammonia even when boiled in diethyl ether.

Triphenylstannylsodium can also be prepared by reaction between sodium–naphthalene and hexaphenyldistannane, triphenyltin bromide, or even tetraphenyltin, in tetrahydrofuran or in 1,2-dimethoxyethane:

$$Ph_3Sn{\cdot}SnPh_3 + 2C_{10}H_8Na \longrightarrow 2Ph_3SnNa + 2C_{10}H_8$$
$$Ph_3SnBr + 2C_{10}H_8Na \longrightarrow Ph_3SnNa + NaBr + 2C_{10}H_8$$
$$Ph_4Sn + 2C_{10}H_8Na \longrightarrow Ph_3SnNa + C_6H_6 + 2C_{10}H_8$$

These reactions are accompanied by vivid colour changes. In the third reaction, which represents a very easy route to triphenylstannylsodium, it is probable that phenylsodium

[3] Gilman and Rosenberg, *J. Org. Chem.*, 1953, **18**, 680.
[4] Gilman and Rosenberg, *J. Org. Chem.*, 1953, **18**, 1554.
[5] Gilman and Rosenberg, *J. Amer. Chem. Soc.*, 1953, **75**, 2507.
[6] Gilman and Swiss, *J. Amer. Chem. Soc.*, 1940, **62**, 1847.

XUM

is formed as a transitory intermediate and reacts at once with solvent. Addition of ethyl bromide to triphenylstannylsodium prepared by these three methods gave ethyltriphenyltin in 75%, 60%, and 65% yield respectively (of purified product).

Gilman and Rosenberg found that tetraphenyltin was commonly a major product of reactions between triphenylstannyl-lithium and alkyl halides. We obtained only insignificant amounts of this product in most of our reactions; for example, ethyl bromide gave 99% of ethyltriphenyltin (by the liquid ammonia method, replacing ammonia by ether) and benzyl chloride gave 88% of benzyltriphenyltin. Reaction with triphenyltin bromide was almost quantitative (95% yield of hexaphenyldistannane).

When an ethereal solution of benzophenone is added to triphenylstannylsodium a bright greenish-blue colour develops at once. This must be due to an electron transfer to the ketone, forming the blue diphenyl ketyl, the greenish tinge being due to the presence of some of the tan-coloured triphenylstannylsodium: $Ph_3Sn^-Na^+ + Ph_2CO \rightleftharpoons \frac{1}{2}Ph_6Sn_2 + Ph_2CO^-Na^+$. Addition of water immediately discharges the colour, and from the reaction mixture were isolated not only benzophenone, as found by Gilman and Rosenberg, but also about an equal weight of diphenylmethanol, a trace of benzpinacol, and hexaphenyldistannane in quantity equivalent to a 75% tin recovery. A similar blue colour, also attributed to ketyl formation, was noted in the complicated reaction between triphenylsilylpotassium and benzophenone.[7] Triphenylgermyl-lithium reacts normally with benzophenone, giving triphenylgermyldiphenylmethanol.[8]

Reaction with benzoyl chloride was more complex, and was accompanied by the transient development of a bright red colour which lasted a few seconds after each addition of benzoyl chloride. This may have been due to the formation of benzoyl radicals or anions. The tin again appeared as hexaphenyldistannane, but no benzil could be detected though it was sought because the reaction mixture was yellow. Instead, the dibenzoate of *cis*-stilbenediol was isolated:

$$Ph{\cdot}COCl + Ph_3SnNa \longrightarrow Ph_6Sn_2 + Ph{\cdot}C(O^-){:}{:}C(O^-)Ph$$

$$Ph{\cdot}C(O^-){:}{:}C(O^-)Ph + 2Ph{\cdot}COCl \longrightarrow Ph{\cdot}C(OBz){:}{:}C(OBz)Ph + 2Cl^-$$

In the last two reactions discussed, triphenylstannylsodium acts only as an electron source, itself being converted into hexaphenyldistannane. This is in contrast to reactions with alkyl halides, in which the distannane is not formed to an appreciable extent. We found a borderline case in reaction with diphenyl disulphide, in which both hexaphenyldistannane and triphenyl(phenylthio)tin are formed:

$$Ph_3SnNa + PhS{\cdot}SPh \longrightarrow Ph_6Sn_2 + Ph_3SnSPh + PhSNa$$

These products were obtained irrespective of the order of mixing of the reactants.

Finally, we report some reactions with simple inorganic compounds, in which triphenylstannylsodium acts only as a reducing agent, hexaphenyldistannane having been the only product containing tin that was isolated. Reaction with gaseous oxygen yields hexaphenylstannane and sodium peroxide (detected only in 50% yield): $2Ph_3SnNa + O_2 \longrightarrow Ph_6Sn_2 + Na_2O_2$.

Carbon dioxide is reduced to oxalate anions, recovered in 98% yield as calcium oxalate, most of the tin again appearing as hexaphenyldistannane: $2Ph_3SnNa + 2CO_2 = Ph_6Sn_2 + Na_2C_2O_4$. Similarly sulphur dioxide gives the distannane (75%) and sodium dithionite (96% by reaction with silver nitrate): $2Ph_3SnNa + 2SO_2 = Ph_6Sn_2 + Na_2S_2O_4$. Alkali-metal amalgams reduce carbon dioxide and sulphur dioxide in a similar way.[9]

Triphenylstannyl-sodium or -lithium is not indefinitely stable in contact with diethyl

[7] Brook and Schwartz, *J. Amer. Chem. Soc.*, 1960, **82**, 2435.
[8] Gilman and Gerow, *J. Amer. Chem. Soc.*, 1955, **77**, 5740.
[9] Hohn, Fitzer, and Nedwed, *Z. anorg. Chem.*, 1953, **274**, 297; Hohn, Fitzer, Chizzola, and Nedwed, *ibid.*, 1954, **275**, 32.

XUM

ether or tetrahydrofuran: hexaphenyldistannane is slowly formed and ethanol (or butanol) was also detected.

Experimental

Microanalyses are by Mr. A. Wiper, of these laboratories. Preparations involving alkali metals or their organic derivatives were carried out in an inert atmosphere.

Triphenyltin bromide was prepared in about 90% yield by heating tetraphenyltin and tin(IV) bromide together for 15 hr. at 220°; propan-1-ol was a convenient solvent for its crystallization, diphenyltin dibromide being freely soluble and tetraphenyltin virtually insoluble in this solvent.

Reactions of Tri-n-butylstannyl-lithium.—Chlorotrimethylsilane. Tri-n-butylstannyl-lithium was prepared by Gilman and Rosenberg's method [2] from tin(II) chloride (17·4 g., 0·092 mole) and n-butyl-lithium in diethyl ether. To this was added, with stirring at −40°, chlorotrimethylsilane (11·5 c.c., 0·092 mole) in ether (100 c.c.). There was no apparent colour change. After removal of ether, volatile products were separated by vacuum-distillation. Fractionation then yielded n-butyltrimethylsilane (6·4 g., 54%), b. p. 116—116·5°, $n_D^{19·5}$ 1·4032 (lit.,[10] b. p. 115·5°, n_D^{20} 1·4030) (Found: C, 65·2; H, 13·75. Calc. for $C_7H_{18}Si$: C, 64·6; H, 13·9%). The involatile residue was orange-red, suggesting the presence of dibutyltin, and extraction by benzene followed by vacuum-distillation gave tetra-n-butyltin (4·3 g.), b. p. 122·5—123·5°/2·9 mm., possibly formed by disproportionation of dibutyltin.

Carbon dioxide. Tri-n-butylstannyl-lithium (0·093 mole) in ether (100 c.c.) was poured on ether and solid carbon dioxide. Oxalate could not be detected in the product, which yielded valeric acid, b. p. 185—187° (3·6 g.; *p*-toluidide, m. p. 71—71·5°), and di-n-butyl ketone, b. p. 185—187° (2·1 g.; semicarbazone, m. p. 89°). The red involatile residue remaining after separation of valeric acid and di-n-butyl ketone contained dibutyltin, since oxidation with 4% aqueous hydrogen peroxide followed by addition of concentrated hydrochloric acid gave di-n-butyltin dichloride, m. p. 39—39·5° (after crystallization from pentane and sublimation; 3·5 g.).

Preparation of Triphenylstannyl-sodium and Reaction with Alkyl Halides.—(A) *The liquid-ammonia method.* Sodium (1·2 g., 0·05 g.-atom) was added, in small pieces, to dry liquid ammonia (100 c.c., distilled from sodium) at −78°. With continuous stirring a suspension of triphenyltin bromide (10·7 g., 0·025 mole) in ether (100 c.c.) was added, quickly at first and later quite slowly to avoid passing appreciably beyond the equivalence point, which is marked by a change from the blue of dissolved sodium through a bright blood-red colour to the pale tan colour of triphenylstannylsodium. The cooling bath was then removed, and most of the ammonia allowed to boil away. More ammonia was removed by pumping at about 20 mm. and then ether (100 c.c.) was added to the yellow-brown residue. Ethyl bromide (2·7 g., 0·025 mole) in ether (50 c.c.) was slowly added with brisk stirring, the mixture being kept at about −60°. Then the mixture was allowed to warm to room temperature and stirred for an hour. Addition of an equal volume of water, separation of the ether phase, and crystallization from methanol of the residue after removal of ether yielded ethyltriphenyltin (8·5 g., 94%), m. p. 55—56° (lit.,[11] m. p. 56°). In similar reactions benzyl chloride yielded benzyltriphenyltin, 80 and 88%, m. p. 90—90·5° from ethanol (lit.,[2] m. p. 90—91°). Ethyltriphenyltin was also prepared in 98% yield by using dimethylformamide instead of diethyl ether as reaction medium.

(B) *The phenyl-lithium method.* Triphenylstannyl-lithium was prepared as previously described.[2]

(C) *The sodium–naphthalene method.* A solution of sodium–naphthalene in 1,2-dimethoxyethane containing 0·027 g.-atom of sodium was added, at 0°, to a stirred suspension of hexaphenyldistannane (0·0135 mole) in the same solvent. The dark green colour of the sodium–naphthalene was rapidly discharged, and the reaction mixture was a deep violet colour when half the sodium–naphthalene had been added. At the equivalence point the colour faded to the pale tan of triphenylstannyl-sodium. Addition of ethyl bromide, removal of naphthalene by steam-distillation, and crystallization of the residue from ethanol gave ethyltriphenyltin (75%).

In a similar but more exothermic reaction using triphenyltin bromide the colour changed from deep green to the final colour through an intermediate magenta. When tetraphenyltin

[10] Bygden, *Ber.*, 1911, **44**, 2640.
[11] Krause and Schmitz, *Ber.*, 1919, **52**, 2150.

XUM

was used initially the colour changed from deep green to blood-red and this persisted even at the equivalence point.

Reactions of Triphenylstannylsodium, etc.—With benzophenone. Benzophenone (4·6 g., 0·025 mole) in ether (50 c.c.) was added to triphenylstannylsodium (0·025 mole) in ether (*ca.* 50 c.c.) at room temperature. The colour changes have already been mentioned. After hydrolysis, filtration yielded hexaphenyldistannane (6·6 g., 75%), and from the yellow ether phase were isolated benzophenone (1·5 g., 33%), diphenylmethanol (1·5 g., 32%), and a trace of benzpinacol (tetraphenylethylene glycol).

With benzoyl chloride. Benzoyl chloride (0·08 mole) in ether (50 c.c.) was slowly added at room temperature to triphenylstannyl-lithium (0·08 mole; prepared by Gilman and Rosenberg's method [2]) in ether (100 c.c.). After hydrolysis, hexaphenyldistannane (20 g., 72%) was recovered, together with a much more soluble product (2·5 g.), identified as the dibenzoate of *cis*-1, 2-stilbenediol (mixed m. p. with authentic specimen prepared by Gomberg and Bachmann's method [12]).

With diphenyl disulphide. Diphenyl disulphide (0·016 mole) in 1,2-dimethoxyethane (22 c.c.) was added to triphenylstannylsodium (0·016 mole, from triphenyltin bromide and sodium–naphthalene) in the same solvent (50 c.c.) at 0°. During the addition the colour changed from light brown through red to a very pale yellow. Next morning the mixture was steam-distilled to remove naphthalene, acidified, and again steam-distilled, yielding thiophenol (2·0 g., identified as 2,4-dinitrophenyl phenyl sulphide, m. p. 120—121°). Extraction of the insoluble residue from the steam-distillation with ethanol gave triphenyl(phenylthio)tin (3·0 g.; m. p. and mixed m. p. 102—103°), and the ethanol-insoluble material when crystallized from benzene gave hexaphenyldistannane (3·4 g., m. p. 229—232°).

In another experiment in which triphenylstannyl-lithium in ether (from phenyl-lithium [2]) was added to an equimolar quantity of diphenyl disulphide in ether, the same products were isolated together with a small amount of unreacted disulphide.

With oxygen. A slow stream of oxygen was passed through triphenylstannylsodium (0·025 mole) in ether (100 c.c.) for 3 hr. A solid product was filtered off (under nitrogen), washed with warm benzene to remove organic matter, and hydrolyzed, giving oxygen (45 c.c. at N.T.P.). A small test sample taken before hydrolysis liberated iodine when added to aqueous potassium iodide. Hexaphenyldistannane (7·0 g.) was recovered from the benzene extract.

With carbon dioxide. Dry carbon dioxide was bubbled through triphenylstannylsodium (0·025 mole) in ether (100 c.c.) during 3 hr. at room temperature; the mixture quickly became colourless. After addition of water, oxalate was determined in the aqueous phase (gravimetrically as calcium oxalate dihydrate, 98%) and hexaphenyldistannane, m. p. 231—232° (7·0 g., 80%), was recovered.

With sulphur dioxide. Dry sulphur dioxide was passed through triphenylstannylsodium (0·01 mole) in 1,2-dimethoxyethane at room temperature for 15 min. The mixture was stored for several hours and then filtered under nitrogen. The residue was washed with ether until there was no trace of sulphur dioxide in the filtrate; it was then washed with warm water into ammoniacal silver nitrate, and the precipitated silver collected, dried, and weighed (1·0533 g., equiv. to 96% of sodium dithionite). Hexaphenyldistannane (2·6 g., 75%) was recovered.

Triphenyl(phenylthio)tin, $Ph_3Sn{\cdot}SPh$.—Thiophenol (12 g.) in dry methanol (20 c.c.) was added to sodium methoxide (5·4 g.) in dry methanol (20 c.c.). Triphenyltin bromide (42 g.) in tetrahydrofuran (50 c.c.) was then added slowly. The mixture was boiled with reflux for 30 min. and filtered; the product crystallized from the filtrate. Recrystallization from ethanol gave colourless *product*, m. p. 103° (37 g., 82%) (Found: C, 62·8; H, 4·5. $C_{24}H_{20}SSn$ requires C, 62·7; H, 4·4%).

Diphenyldi(phenylthio)tin, $Ph_2Sn(SPh)_2$.—This was similarly prepared from diphenyltin dibromide, and crystallized from ethanol as colourless needles, m. p. 66—67° (Found: C, 58·3; H, 4·3. $C_{24}H_{20}S_2Sn$ requires C, 58·6; H, 4·1%).

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South Road, Durham. [*Received, September 1st*, 1960.]

[12] Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1927, **49**, 2587.

125. *The Structure of Isolichenin.*

By Stanley Peat, W. J. Whelan, J. R. Turvey, and K. Morgan.

Isolichenin is isolated in an improved yield from Iceland moss by a modification of the method of Chanda, Hirst, and Manners, whose report that isolichenin is constituted solely of glucose units united by 1,4- and 1,3-linkages is confirmed by the method of partial acid hydrolysis. It is further shown that these linkages have the α-configuration inasmuch as maltose and nigerose are components of the partial hydrolysate.

There is some lack of regularity in the distribution of the α-1,3- and α-1,4-links in isolichenin although the detection of nigerotriose and maltotriose in the trisaccharide fraction of the acid hydrolysate shows that both types of linkage can occur at least in pairs. No evidence is forthcoming that branching occurs in isolichenin.

It is further established that isolichenin is not identical with nigeran, in which there is an alternation of α-1,4- and α-1,3-links. Nevertheless the ratio of 1,3- to 1,4-links (55 : 45) in isolichenin is not far removed from that in nigeran (approx. 50 : 50).

The lichenin of Iceland moss (*Cetraria islandica*) is accompanied by isolichenin, and it was early recognised that, while lichenin itself was cellulosic in character, isolichenin partook more of the nature of starch in respect of its iodine-staining power and its susceptibility to diastatic action. Indeed it was originally named " lichen-starch " and was regarded as a food-reserve material.[1] Later investigations[2,3] revealed that lichen-starch was a mixture of polysaccharides and in its acid hydrolysate mannose and galactose were found in addition to glucose. The name isolichenin is now restricted to the iodophilic polyglucose component of this mixture, from which it was separated in a pure state by Chanda, Hirst, and Manners.[4] Our specimen of isolichenin was prepared, in improved yield, by a modification of the method described by these authors, about which we had knowledge before its publication, through the courtesy of Professor E. L. Hirst.

The study reported here of the structure of isolichenin followed as a consequence of the investigation of lichenin [5] and the same method of linkage analysis was adopted, namely, examination of the products of partial acid hydrolysis.

The purified isolichenin (57 g. from 5 kg. of tannin-free moss) gave with iodine a grey-blue colour of low intensity (the blue value [6] was 0·005) and showed the exceptionally high specific rotation in water of $[\alpha]_D$ +272° (lichenin from the same moss had $[\alpha]_D$ +18·4° in 2N-sodium hydroxide [5]). Complete acid-hydrolysis yielded glucose as the sole carbohydrate product.

Partial Acid-hydrolysis.—The Kuhn formula [7] indicates that the maximum yield of di- and tri-saccharide fragments should be attained at an apparent conversion into glucose of about 45%. Accordingly, isolichenin (38 g.) was submitted to hydrolysis with 0·33N-sulphuric acid until the apparent conversion was 43%. The neutralised hydrolysate was fractionated by graded elution with ethanol on a charcoal–Celite column. The sole monosaccharide component of the hydrolysate was glucose.

The disaccharide fraction. Ionophoresis in borate buffer demonstrated the presence of two disaccharides, which were chromatographically separated on charcoal with an ethanol–borate eluant.[8] The first to be desorbed had a relatively high electrophoretic

[1] Hönig and Schubert, *Monatsh.*, 1887, **8**, 452.
[2] Karrer and Joos, *Z. physiol. Chem.*, 1924, **141**, 311.
[3] Meyer and Gürtler, *Helv. Chim. Acta*, 1947, **30**, 761.
[4] Chanda, Hirst, and Manners, *J.*, 1957, 1951.
[5] Peat, Whelan, and Roberts, *J.*, 1957, 3916.
[6] Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924.
[7] Kuhn, *Ber.*, 1930, **63**, 1503.
[8] Barker, Bourne, and Theander, *J.*, 1955, 4276.

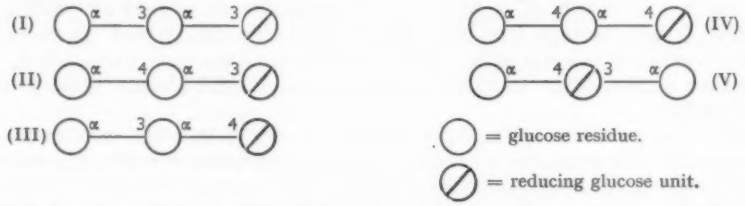
XUM

mobility (M_G 0·55) and was shown by comparison of its properties, and those of its β-octa-acetate, with authentic specimens (Table 1) to be nigerose (3-*O*-α-glucosylglucose). The slower-moving component was proved in the same way to be maltose. The yield of nigerose (3·4 g.) was approximately double that of maltose (1·55 g.). These yields can, of course, not be regarded as more than a rough estimate of the relative proportions of α-1,3- and α-1,4-linkages in isolichenin since the yields of nigerose and maltose will be determined in part by the relative rates of hydrolysis of the α-1,4- and α-1,3-links, respectively. It is improbable that the two disaccharides are formed in these quantities by acid-reversion from glucose. They have been obtained as reversion products in very small amounts but they are accompanied by isomaltose and gentiobiose in substantially greater amounts.[9,10] Neither of these 1,6-linked disaccharides was detected in the isolichenin hydrolysate. It was thus established that in isolichenin the polymeric linkages are of α-1,3- and α-1,4-glucosidic types, and that very probably these are the only forms of glucosidic linkage.

The trisaccharide fraction. Paper chromatography having revealed the presence of at least two reducing trisaccharides with closely similar R_F values, the whole fraction was separated into two subfractions, *A* and *B*, by elution from a charcoal column, initially with ethanol–borate,[8] and subsequently with aqueous ethanol. Each of the fractions moved ionophoretically as a single substance, *A* with high (M_G 0·55) and *B* with low mobility (M_G 0·21).

Since the examination of the disaccharide fraction had shown only maltose and nigerose to be present, it could be inferred that the reducing-end linkage in *A* (high mobility) was of the 1,3-type and in *B* (low mobility) was the 1,4-type. When materials *A* and *B* were partly hydrolysed with acid and examined by ionophoresis the hydrolysate of *A* contained glucose (M_G 1·0) and a substance having M_G 0·21, presumably maltose, as well as the expected nigerose. The hydrolysate of *B* contained glucose and a substance having M_G 0·55, presumably nigerose, as well as the expected maltose. It was thus evident that both reducing trisaccharide subfractions contained the same linkages, *viz.*, an α-1,4- and an α-1,3-link, and differed only in the order and arrangement of these linkages.

If it is assumed that isolichenin has an unbranched structure, and there are some grounds for this, the possible trisaccharides derivable from it would be nigerotriose (I), 3-α-maltosylglucose (II), 4-α-nigerosylglucose (III), and maltotriose (IV).



The reducing end glucose units in (I) and (II) carry free hydroxyl groups at positions 2 and 4 and would therefore form strong borate complexes [11] showing relatively high electrophoretic mobility, whereas (III) and (IV), in which the 4-hydroxyl group is blocked, would form weak borate complexes with low electrophoretic mobility. It follows from the method of separation of the trisaccharides that *A* could be a mixture of (I) and (II), and *B* a mixture of (III) and (IV) if all four possible trisaccharides were present. Although the trisaccharide fractions *A* and *B* moved electrophoretically as if each were a single substance, the following observations made it evident that each was in fact a mixture of trisaccharides. The materials *A* and *B* were separately reduced with sodium borohydride to the corresponding trisaccharide alcohols, *RA* and *RB*. The reducing end glucose unit

[9] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[10] Peat, Whelan, Edwards, and Owen, *J.*, 1958, 586.

in each of the four possible trisaccharides (I—IV) would by this procedure be converted into a non-reducing sorbitol unit. These alcohols will be designated (RI—RIV) respectively. The products of partial acid-hydrolysis of the trisaccharide alcohols would consist of reducing disaccharides and non-reducing disaccharide alcohols as well as glucose and sorbitol. (RI) would give nigerose and nigeritol; (RII) maltose and nigeritol; (RIII) nigerose and maltitol; and (RIV) maltose and maltitol. Under the conditions of hydrolysis employed, no assay of the disaccharide alcohols could be made, but it was shown that the alcohol *RA* yielded two reducing disaccharides which had the electrophoretic mobility (M_G) of maltose and nigerose, derived respectively from (RI) and (RII). Two reducing disaccharides, *viz.*, maltose and nigerose, were also obtained by the partial acid hydrolysis of the alcohol *RB* and these must have come from (RIV) and (RIII) respectively. It appears therefore that there exists some degree of lack of regularity in the distribution of α-1,3- and α-1,4-links in isolichenin, inasmuch as the four trisaccharides (I—IV) are integral parts of the chain molecule. It should be pointed out that the "branched" trisaccharide (V) was not detected in the partial hydrolysate of isolichenin and, although this negative evidence is not strong, it is an indication that the isolichenin chains are not branched.

Structure of Isolichenin.—The experiments reported here confirm the observations by Chanda *et al.*[4] that isolichenin is a polymer of D-glucose joined through 1,3-linkages and 1,4-linkages. It is further shown that these linkages are exclusively in the α-configuration and the arrangement of the linkages is to some extent shown by the components of the trisaccharide fraction of the partial hydrolysate. The proof that two trisaccharides containing 1,4- and 1,3-linkages were present means that both linkages occur in the same polymer molecule. The detection of nigerotriose and maltotriose among the trisaccharides means that the two types of linkage can occur at least in pairs. It is not apparent, however, whether any regularity exists in the structure but experiments to be reported later by Goldstein and Whelan show that a regular repeating sequence of linkages may well be present.

The slight action of α- and β-amylase on isolichenin, as shown by loss of iodine staining power, and the slight development of reducing power, could be cited as evidence for the occurrence of sequences of α-1,4-linkages in isolichenin, but an alternative explanation might well be that isolichenin is contaminated by a starch-like substance and it is this which is responsible for these effects. None of the stages of purification of the isolichenin would be expected to remove a starch component but fractionation experiments designed to do this are now being attempted.

These experiments establish that isolichenin is not identical with nigeran, which is also constituted of glucose units joined by α-1,4- and α-1,3-links only, and which shows an optical rotation (+283°) of the same high order as isolichenin.[12-14] Approximately half of the glucosidic links in nigeran are α-1,4- and the pattern is an ordered alternation of α-1,4- and α-1,3-links.

It will be noted that if the ratio of 1,3- to 1,4-links in isolichenin is also 1 : 1, then approximately equal weights of trisaccharides *A* and *B* would have been produced. Actually the weight ratio was 2 : 1, agreeing with the similar weight ratio of the disaccharides, nigerose : maltose.

A more accurate estimate of the ratio of 1,3- to 1,4-links can be obtained by oxidation of the polysaccharide with periodate. Accordingly, isolichenin was treated with unbuffered sodium metaperiodate at room temperature and in the dark. The initial rapid uptake of oxidant was followed by a much slower rate of overoxidation of the malonyl residue at the reducing end of the polysaccharide chain. The amount of periodate consumed at the

[11] Foster, *J.*, 1953, 983.
[12] Barker, Bourne, and Stacey, *Chem. and Ind.*, 1952, 756.
[13] Barker, Bourne, and Stacey, *J.*, 1953, 3084.
[14] Barker, Bourne, O'Mant, and Stacey, *J.*, 1957, 2448.

XUM

point of inflexion in the oxidation curve was taken as a measure of the degree of normal oxidation. A glucose unit linked at position 3 as well as at position 1 is not susceptible to oxidation by periodate so that the uptake of periodate during the initial rapid oxidation must be due to the glucose members linked through $C_{(1)}$ and $C_{(4)}$ and, of course, to the end groups. On this basis, it is calculated that the ratio of 1,3- to 1,4-links in isolichenin is 55 : 45, a result in fair agreement with that found by Chanda *et al.* (60 : 40), also by periodate oxidation.[4] The discrepancy between this result and the weight ratio of nigerose to maltose (2 : 1) may be ascribed, as mentioned above, to a slower hydrolysis of the α-1,3-links and the consequent preferential accumulation of nigerose in the partial acid-hydrolysate.

Experimental

Purification of Isolichenin.—The water-soluble polysaccharides from Iceland moss were extracted by the method of Meyer and Gürtler,[15] which is originally due to Hess and Lauridsen.[16] Tannins were removed from air-dried Iceland moss (1 kg.) by six extractions, each for 24 hr., with cold 2% potassium carbonate solution (17 l.), and the moss was then washed with water until free from alkali.

The tannin-free moss (1 kg.) was extracted with water (6 l.) at 95—98° for 24 hr., and filtered hot through muslin. The residual moss was extracted twice with water (2 × 6 l.) in an autoclave at 15 lb. pressure for 1 hr.; this ensured almost complete extraction of iodine staining material (blue) from the moss. The filtrates were combined (total 18 l.).

The combined extracts from five 1 kg. batches of moss were frozen and thawed three times [17] and the lichenin was removed by filtration and centrifugation. The supernatant liquid was concentrated to a viscous liquid (7 l.) and dialysed in a Cellophane bag (6 cm. in diameter) against water to remove salts and possible saccharides of low molecular weight. The solution of impermeable materials was concentrated to 4 l. and the polysaccharides precipitated by the slow addition of acetone (5 l.). The precipitate, isolichenin A, was collected in a centrifuge, washed with acetone and alcohol, and hardened by grinding under ether (dry wt., 195 g.). The crude isolichenin, dissolved in water (1 l.), was treated with Fehling's solution (1·2 l.) until the supernatant liquid was deep blue. A flocculant precipitate was discarded and the mother-liquor acidified to pH 4·5 with 3N-acetic acid (900 ml.). Sufficient acetone (*ca.* 4 l.) was then added to ensure complete precipitation of the polysaccharide. The centrifuged precipitate, dissolved in water (2 l.), was poured slowly, with stirring, into ethanol (8 l.). The dried precipitate (110 g.) was dissolved in water (1 l.), acidified to pH 3·9 with 3N-acetic acid, and again precipitated by slow addition of acetone (800 ml.). This precipitate (66 g.) was dried and dissolved in water (1 l.), and the viscous solution was poured slowly into ethanol (4 l.). The polysaccharide was thus precipitated as a white fibrous material and was separated by centrifugation, washed, and dried in the usual manner (yield, 57 g.). The specimens showed $[\alpha]_D$ +272° (*c* 0·49 in H_2O) and blue value 0·0054, and gave no ash. In the hydrolysate of a portion (15 mg.) with 0·33N-sulphuric acid (1 ml.) only glucose was detected by paper chromatography.

Hydrolysis.—Isolichenin (38·4 g., based on carbohydrate content [18]) was dissolved in hot water (3733 ml.) and mixed with 5N-sulphuric acid so that the final acid concentration was 0·33N and the polysaccharide concentration about 1%. The solution was heated at 100° and portions (2 ml.) were withdrawn at intervals, neutralised with aqueous sodium hydroxide, and diluted to 25 ml., and the reducing powers (as glucose) of 5 ml. portions were determined with the Somogyi copper reagent.[19]. The hydrolysis was arrested after 75 min. by neutralisation with 3N-sodium hydroxide; the reducing power then corresponded to an apparent conversion into glucose of 42·5%.

Fractionation of the Hydrolysis Products.—The neutralised hydrolysate was concentrated to about 1·8 l., and added to a charcoal–Celite column (5 × 203 cm.). The column was irrigated under pressure, applied by a constant head of eluant some 15 ft. above the top of the

[15] Meyer and Gürtler, *Helv. Chim. Acta*, 1947, **30**, 751.
[16] Hess and Lauridsen, *Ber.*, 1940, **73**, 115.
[17] Ulander and Tollens, *Ber.*, 1906, **39**, 401.
[18] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.
[19] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.

column, first with water and then by graded elution [20] with ethanol, 20% ethanol being allowed to flow into a mixing chamber containing water (15 l.). The optical rotation of each fraction (volume 250 ml.) was measured in a 4 dm. tube. The appropriate fractions were combined and evaporated under diminished pressure at 40°.

Examination of the Hydrolysis Products.—The fractions were combined as indicated and evaporated to dryness *in vacuo*. Concentrations of isolechenin solutions for quantitative analyses were determined by complete hydrolysis to glucose.[18]

The solvent systems used for descending paper chromatography were butan-1-ol–acetic acid–water (4 : 1 : 5, by vol.), and propan-1-ol–ethyl acetate–water (6 : 1 : 3, by vol.). It was usual to examine a sugar fraction in each of these solvents on Whatman no. 54 paper and to locate the component(s) with benzidine–trichloroacetic acid [21] (reducing sugars) and silver nitrate–sodium hydroxide [22] (reducing and non-reducing sugars).

(a) *Monosaccharide.* Paper chromatographic examination of the combined fractions nos. 25—43 showed the presence of a single reducing sugar which migrated with an R_F value corresponding to that of glucose. The sugar, crystallised from methanol, had m. p. 145—146° and $[\alpha]_D$ +52·5° (equilibrium value in H_2O).

(b) *Disaccharides.* A portion of fractions nos. 91—120 was shown by paper chromatography to contain two disaccharides, each migrating with an R_F value close to that of maltose, and ionophoresis in borate buffer [8] (pH 8·7) showed the presence of two components, one with a high and the other with a low ionophoretic mobility.

The disaccharide mixture (about 10 g.) was dissolved in water (about 100 ml.) and adsorbed on a charcoal–Celite column (5 × 75 cm.). The column was eluted by adding a 10% solution of ethanol in water containing also sodium borate (0·572 %) and boric acid (0·247%) (pH 8·7), into a mixing chamber containing 10 l. of aqueous sodium borate (0·572%) and boric acid (0·247%), which led to the column. The optical rotations of the fractions (*ca.* 100 ml.) were measured and the elution curve so obtained showed two elution peaks. The fractions embracing these peaks, namely, nos. 21—54 and nos. 55—90, were combined and brought to pH 5 with dilute sulphuric acid. Each batch was concentrated to small volume and adsorbed on charcoal–Celite columns (4 × 93 cm.). The columns were eluted, first with water to remove borate ions, and then with 7·5% of ethanol in water. Appropriate fractions were combined in each case and evaporated to dryness. Each residue was then extracted with boiling 80% methanol (75 ml.; 2 × 25 ml.), and the combined methanolic extracts were evaporated to dryness.

Paper chromatography showed each fraction to be homogeneous. Ionophoresis in borate buffer of pH 8·7 showed disaccharide (I) to have M_G 0·55 and disaccharide (II) M_G 0·21. In borate buffer [11] of pH 10·0 nigerose has M_G 0·69 and maltose M_G 0·32.

TABLE 1. *Properties of sugars and their derivatives isolated from a partial acid-hydrolysate of isolichenin.*

	Experimental values			Authentic values			
		β-Octa-acetate			β-Octa-acetate		
Sugar	$[\alpha]_D$ (equil. in H_2O)	$[\alpha]_D$ in chloroform	M. p.	$[\alpha]_D$ (equil. in H_2O)	$[\alpha]_D$ in chloroform	M. p.	Ref.
Glucose ...	+52·5°	—	—	+52·7°	—	—	*a*
Maltose ...	+135·6	+63·9°	158—159	+136	+62·6°	159—160	*a*
					+80·0	151—153	*b*
Nigerose...	+138·8	+84·9	149	+136	+75·7	151—153	*c*
					+78·0	155—157	9

(*a*) Bates, " Polarimetry and Saccharimetry," 1942, Nat. Bureau Stand., Washington. (*b*) Wolfrom, *J. Amer. Chem. Soc.*, 1955, **77**, 6403; Matsuda and Aso, *J. Fermentation Technol. (Japan)*, 1954, **32**, 399. (*c*) Peat, Whelan, and Hinson, *Chem. and Ind.*, 1955, 385.

The β-octa-acetates of the two disaccharides were prepared by reaction with sodium acetate–acetic anhydride,[23] and the properties are reported in Table 1 (Found, for β-nigerose octa-acetate: C, 49·9; H, 5·6. For β-maltose octa-acetate: C, 49·5; H, 5·9. Calc. for $C_{28}H_{38}O_{19}$: C, 49·5; H, 5·9%).

[20] Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826; Alm, *ibid.*, p. 1186.
[21] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114.
[22] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 44.
[23] Erwig and Koenigs, *Ber.*, 1889, **22**, 2207.

XUM

(c) *Trisaccharides.* The trisaccharide mixture (2·30 g., air-dried) from the isolichenin hydrolysate, dissolved in water (*ca.* 50 ml.) and adsorbed on a charcoal–Celite column (3·8 × 52 cm.), was eluted with ethanol–borate buffer (pH 8·7) by allowing 10% ethanol (in borate buffer, pH 8·7, see above) to flow into a mixing chamber containing borate buffer, pH 8·7 (4 l.). Fractions (100 ml.) were collected, their optical rotations were measured, and the elution curve was plotted. Two definite elution peaks were obtained but these were incompletely separated. Trisaccharide batch A (fractions nos. 25—59) and trisaccharide batch B (fractions nos. 71—94) were separately acidified to pH 5 with dilute sulphuric acid, concentrated to a small volume, and adsorbed on charcoal–Celite (3·8 × 38 cm.). The column was eluted with water until removal of the borate ions was complete and then with 15% ethanol. Fractions (100 ml.) were collected and the respective elution curves plotted. The appropriate fractions were combined in each case and evaporated to dryness. Each residue, A and B, was then extracted with boiling 80% methanol (75 ml., 25 ml.) and the combined methanolic extracts were evaporated to dryness.

Trisaccharide A was shown by ionophoresis in borate buffer (pH 8·7) to contain a single reducing component with M_G 0·55. A portion (15·8 mg.) was partially hydrolysed by being heated in a water-bath with 0·33N-sulphuric acid (1 ml.) for 40 min. Ionophoresis of the hydrolysate in a borate buffer (pH 8·7) revealed the presence of two components: one had M_G 0·21 corresponding to that of a maltose control; the other had M_G 0·55 corresponding to that of a nigerose control. The component with M_G 0·55 was present in appreciably greater amount.

Trisaccharide A (226 mg.) was mixed with sodium borohydride (238 mg.) in water (10 ml.) and kept at room temperature for 24 hr. (cf. ref. 24). The solution was then acidified to pH 5 with 3N-acetic acid. After removal of the borate ions on a small charcoal–Celite column (1·8 × 25 cm.), the trisaccharide alcohol was eluted (25 ml. fractions) with 15% ethanol. Fractions containing the reduced trisaccharide were evaporated to dryness, the residue was extracted with boiling 80% methanol (25 ml., 2 × 20 ml.) and the combined extracts were evaporated to dryness (yield, 205 mg.). Paper chromatography revealed the presence of a non-reducing substance having an R_F value corresponding approximately to that of a trisaccharide.

A portion (15 mg.) of this reduced material *RA* was heated with 0·33N-sulphuric acid (1 ml.) in a boiling-water bath for 40 min. Ionophoretic examination of the cooled hydrolysate showed the presence of glucose and reducing components with M_G 0·21 (corresponding to maltose) and M_G 0·55 (corresponding to nigerose).

Trisaccharide B moved ionophoretically as a single substance with M_G 0·21. Ionophoretic examination of a partial acid-hydrolysate of the mixture revealed the presence of two components, one migrating with a high (0·55) and the other with a low (0·21) mobility. These values corresponded to those for authentic nigerose and maltose respectively.

Trisaccharide B was reduced with sodium borohydride, and the alcohol mixture so obtained was partially hydrolysed in 0·33N-sulphuric acid. Examination of the hydrolysate by ionophoresis revealed components identical with those detected in a partial acid-hydrolysis of trisaccharide A.

Periodate Oxidation of Isolichenin.—Isolichenin (1·123 g.) was dissolved in water (*ca.* 180 ml.), 0·25M-sodium metaperiodate (50 ml.) was added, and the solution diluted to 250 ml. The solution was stored in the dark at 19°. A control solution also was prepared by diluting 0·25M-sodium metaperiodate (50 ml.) to 250 ml.

At intervals, a portion (3 ml.) of the reaction mixture was removed and diluted with water (*ca.* 50 ml.). 10% w/v Potassium iodide solution (3 ml.) and 2N-sulphuric acid (2 ml.) were

TABLE 2.

Time of oxidn. (hr.).....	0·33	1·0	1·5	10	21	51	78	117	165	261	286
$NaIO_4$ consumed (mole per $C_6H_{10}O_5$)	0·411	0·421	0·435	0·449	0·453	0·465	0·471	0·485	0·501	0·533	0·543

then added, the mixture was shaken, and the liberated iodine titrated immediately with N/30-sodium thiosulphate. A portion (3 ml.) of the control digest was similarly treated. Results are in Table 2.

[24] Abdel-Ahker, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691; Whelan and Morgan, *Chem. and Ind.*, 1955, 1447.

Action of Salivary α-Amylase on Isolichenin.—Human saliva (25 ml.) was diluted with an equal volume of water, and the mixture centrifuged to remove the mucins. The supernatant liquid was then used as the source of α-amylase.

(i) *Diminution in iodine-staining power.* A digest of isolichenin (437 mg.), 50% human saliva (10 ml.), and 0·2M-citrate buffer (10 ml.) in water (100 ml.) was incubated at 35° and after about 2 hr. more saliva (5 ml.) was added. Aliquot parts (5 ml.) were withdrawn at intervals, mixed with " Spekker " iodine (2 ml.) and three drops of 3N-hydrochloric acid, and diluted with water to 100 ml. The absorption value (at 680 mμ) was measured on a Spekker photoelectric absorptiometer.[6]

Time of digestion	0	2 min.	5 min.	12 min.	25 min.
Absorption value	0·228	0·108	0·100	0·089	0·079
Time of digestion	3 hr.	6 hr.	19 hr.	35 hr.	
Absorption value	0·042	0·035	0·016	0·006	

The measurement at zero time was made on 5 ml. of the original polysaccharide solution and corresponds to a blue value [6] of 0·0052.

(ii) *Increase in reducing power.* A digest of isolichenin (253 mg.), 50% saliva (5 ml.), and 0·2M-citrate buffer, diluted to 50 ml., was incubated at 35° and after about 2 hr. a further 5 ml. of saliva was added to the digest. Aliquot parts (5 ml.) were withdrawn at intervals and the apparent conversion into maltose determined by the Somogyi method: [19]

Time	0	7 min.	15 min.	3·5 hr.	8·5 hr.	24·5 hr.	34·5 hr.	48·5 hr.
Apparent conversion into maltose (%) ...	1·26	1·36	1·36	2·50	3·30	3·90	3·96	4·26

(iii) *Products of α-amylolysis of isolichenin.* A digest of isolichenin (about 500 mg.), 50% saliva (*ca.* 50 ml.), and 0·2M-citrate buffer (10 ml.) in 100 ml. was incubated at 35° for 48 hr. The enzyme was inactivated by heating it at 100° for 5 min. A portion (about 20 ml.) of the solution was poured into ethanol (4 vol.) to remove protein and salts, and the mixture was centrifuged. The supernatant liquid was evaporated to dryness and analysed by paper chromatography. Maltose, maltotriose, and glucose were detected on the chromatogram, maltose being present in the largest quantity.

Action of Soya-bean β-Amylase on Isolichenin.—A portion (0·5 ml.) of a stock soya-bean β-amylase solution (1 ml., 4000 units [25]) was diluted to 25 ml. with 0·2M-acetate buffer [pH 4·8; prepared by dissolving hydrated sodium acetate (32·64 g.) and glacial acetic acid (9·6 g.) in water and dilution to 2 l.].

(i) *Iodine-staining powder.* An aliquot part (50 ml.) of the isolichenin solution (891 mg./100 ml.) with β-amylase solution (25 ml.), diluted to 100 ml., was incubated at 35°. Aliquot parts (5 ml.) were withdrawn from the digest at intervals and the absorption values determined as described previously.

Time of digestion	0	15 min.	30 min.	45 min.	1·0 hr.
Absorption value	0·257	0·170	0·159	0·163	0·159
Time of digestion	1·25 hr.	1·5 hr.	15 hr.	42 hr.	
Absorption value	0·163	0·170	0·152	0·152	

The value at zero time was measured on the original polysaccharide solution and corresponded to a blue value of 0·0058.

(ii) *Reducing power of the digest.* A reducing-power determination [19] was made on a portion (5 ml.) of the digest after the absorption value had become constant, *i.e.*, after 24 hr. Duplicate samples gave values for the apparent conversion into maltose of 0·45% and 0·58%.

(iii) *Products.* Isolichenin (*ca.* 500 mg.) was digested at 35° with " stock " soya-bean β-amylase (0·3 ml.) in a solution (100 ml.) of pH 4·8. After 48 hr. the enzyme was inactivated at 100° (5 min.). A portion of the cooled solution was then treated as described above and the residue analysed by paper chromatography. Maltose was the only sugar detected on the chromatogram.

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[25] Pirt, Ph.D. Thesis, University of Wales, 1950.

XUM

126. *Oxidations of Organic Compounds with Quinquevalent Vanadium. Part VII.*[1] *The Kinetic Resemblance between the Oxidations of some α-Hydroxy-acids and that of Pinacol and of its Monomethyl Ether.*

By J. R. Jones, William A. Waters, and (in part) J. S. Littler.

Lactic, malic, and mandelic acid are oxidised by vanadium(v) according to the reaction:

$$R{\cdot}CH(OH){\cdot}CO_2H + 2V^{V} \longrightarrow R{\cdot}CHO + H_2O + CO_2 + 2V^{IV}$$

at a rate given by

$$-d[V^{V}]/dt = k[\text{Hydroxy-acid}][V^{V}](1 + ah_0)$$

where h_0 is the Hammett acidity function. This rate equation also holds for oxidation of pinacol in perchloric acid solutions of constant ionic strength, but the rate of oxidation of pinacol monomethyl ether depends on the acid concentration. The reason for this difference is discussed.

Levesley and Waters [2] showed that in many respects the oxidations of α-hydroxy-acids by manganic pyrophosphate resemble that of pinacol. We have now examined the oxidation of lactic, malic, and mandelic acid by quinquevalent vanadium in perchloric acid solution and again find that the oxidations involve C–C bond fission and are kinetically similar to that of pinacol. All three α-hydroxy-acids quickly consume 2 equivalents of vanadium(v), as required by the reaction:

$$R{\cdot}CH(OH){\cdot}CO_2H + 2V^{V} \longrightarrow R{\cdot}CHO + H_2O + CO_2 + 2V^{IV}$$

and the aldehydic products are thereafter oxidised more gradually. Both lactic and malic acid yield some acetaldehyde, and mandelic acid gives benzaldehyde.

Kinetic measurements carried out in perchloric acid–sodium perchlorate mixtures of constant ionic strength are summarised in the Tables which follow. They show that the oxidations are all of first order with respect both to vanadium(v) and to the α-hydroxy-acid. In contrast to the oxidations effected by manganic pyrophosphate,[2,3] no kinetic evidence for initial complex formation between the vanadium and the α-hydroxy-acid could be discerned, but this is not surprising since oxidation of cyclohexanol [4] by vanadium(v), in which complex formation is involved, shows no deviation from first-order kinetics with respect to the alcohol. The addition of manganous ions had no effect on the rate of the reaction (cf. ref. 2).

The α-hydroxy-acids resemble pinacol in being oxidised by quinquevalent vanadium at a rate that can be expressed by equation (*A*)

$$-d[V^{V}]/dt = k[\text{Substrate}][\text{Vanadium(v)}](1 + ah_0) \quad . \quad . \quad . \quad . \quad (A)$$

where h_0 is the appropriate value of the Hammett acidity function.

This type of acidity-dependence for the oxidation rate of pinacol was suggested by Littler and Waters [5] who however did not control the ionic strengths of their solutions and used sulphuric acid, which itself forms complexes with vanadium(v). Table 2(*d*) shows that the oxidation of pinacol in perchloric acid at constant ionic strength follows equation (*A*) but Table 3 shows that the rate of oxidation of pinacol monomethyl ether has dependence on the acidity concentration, $C_{H_3O^+}$. Comparison of Table 1(*a*) with 1(*b*) and of Table 1(*c*) with 1(*d*) shows that the positive ionic-strength effect is considerable in

[1] Part VI, *J.*, 1960, 2773.
[2] Levesley and Waters, *J.*, 1955, 217.
[3] Drummond and Waters, *J.*, 1953, 2836.
[4] Littler and Waters, *J.*, 1959, 4046.
[5] Littler and Waters, *J.*, 1959, 1299.

this type of oxidation. This accords with the view that the reacting species is a doubly charged cation (III).

TABLE 1. *Oxidation of α-hydroxy-acids by vanadium*(V): *reaction order with respect to the α-hydroxy-acid.*

(*a*) Lactic acid in 1·0N-perchloric acid; ionic strength, S = 3M.

Hydroxy-acid (N)	0·110	0·219	0·274	0·329	0·384	0·439
k (10^{-4} sec.$^{-1}$)	1·18	2·62	3·27	4·03	4·73	5·25
10^4k/[Acid]	10·8	11·1	12·2	12·3	12·3	12·0

(*b*) Lactic acid in 3·0N-perchloric acid; ionic strength S = 3M.

Hydroxy-acid (N)	0·086	0·161	0·240	0·320	0·400
k (10^{-4} sec.$^{-1}$)	3·77	7·60	11·1	15·8	19·0
10^4k/[Acid]	47·1	47·5	46·3	49·4	47·5

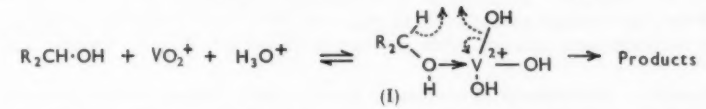
(*c*) Malic acid in 1·0N-perchloric acid; no added salt.

Hydroxy-acid (N)	0·078	0·156	0·233	0·311	0·389
k (10^{-4} sec.$^{-1}$)	1·05	2·17	3·30	4·53	5·60
10^4k/[Acid]	13·5	13·9	14·2	14·6	14·4

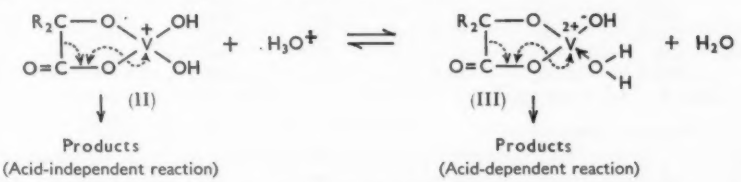
(*d*) Malic acid in 3·0N-perchloric acid; no added salt.

Hydroxy-acid (N)	0·078	0·156	0·233	0·311	0·389
k (10^{-4} sec.$^{-1}$)	4·22	10·0	14·4	19·5	24·0
10^4k/[Acid]	54·1	64·1	61·8	62·7	61·7

Now the oxidations of cyclohexanol and of those secondary α-glycols which are attacked at C–H bonds [6] have been found to be linearly dependent on hydrogen-ion concentration, $C_{H_3O^+}$, and not on the Hammett function, h_0. For the alcohol oxidation it has been suggested [4] that the reactive complex has a structure (I) in which both a monohydric alcohol molecule and a hydrated proton are co-ordinated to the VO_2^+ cation.



However, in the oxidation of both the pinacol and the α-hydroxy-acid the complexes (II) and (III), which can undergo C–C fission, need not contain an extra water molecule, for the protonated structure (III) postulated for the acid-catalysed reaction can be built up from VO_2^+, a substrate molecule, and a proton.



If this is so, Hammett's original theories [7] of the differing kinetic significance of h_0 and $C_{H_3O^+}$ satisfactorily explain why the rate of acid-dependent oxidation of hydroxy-acids and of pinacol follows h_0 rather than $[H_3O^+]$, and why the rate of oxidation of pinacol monomethyl ether follows $[H_3O^+]$ and not h_0, for the latter would form a complex of type (IV) (cf. I). This is in agreement with the stereochemical evidence of Part IV [8] and the kinetic data of Part V.[6]

We suggest that the reversible formation of complexes (II—IV) precedes the rate-determining, concerted electron redistribution which, in converting vanadium(V) into

[6] Littler and Waters, *J.*, 1960, 2767.
[7] Hammett, "Physical Organic Chemistry," Chap. ix, McGraw-Hill Publ. Co., New York, 1940.
[8] Littler, Mallet, and Waters, *J.*, 1960, 2761.

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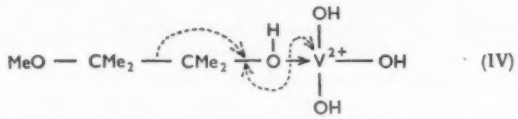
vanadium(IV), effects C–C fission giving radicals, $R_2C(OH)\cdot$ or $R_2C(OMe)\cdot$, which are then rapidly oxidised further.



(IV)

In support of our view that α-hydroxy-acids form soluble complexes with quinquevalent vanadium we have observed that, though the gradual acidification of aqueous ammonium metavanadate with solutions of lactic, malic, acetic, and monochloroacetic acid leads in all cases to the separation of a brown precipitate (V_2O_5 polymer), the latter is easily soluble in an excess of each of the hydroxy-acids but is not dissolved by further aqueous acetic or monochloroacetic acid, though the latter has a pK_a similar to those of the hydroxy-acids. These solutions of vanadium(V) in an excess of lactic or malic acids do very slowly ($k \approx 0{\cdot}1 \times 10^{-4}$ sec.$^{-1}$ at 25°) reduce ammonium vanadate without the addition of any mineral acid: they could contain low concentrations of charged complexes (II).

Experimental and Results

Materials.—Lactic acid was of "AnalaR" grade; (±)-malic acid was crystallised from ethyl acetate to m. p. 128°, and (±)-mandelic acid from benzene to m. p. 118°. The concentrations of these acids in distilled water at the thermostat temperature were determined by titration with sodium hydroxide. Pinacol monomethyl ether (cf. Part V [6]) was purified by vapour-phase chromatography through Apiezon grease on Embacil at 100° and was obtained free from pinacol dimethyl ether.

Mixtures of "AnalaR" ammonium metavanadate, perchloric acid (Harrington's 60%, diluted to 8·0M), and sodium perchlorate (Hopkin and Williams, recrystallised grade, in 8·0M-solution) of constant ionic strength were warmed to 25° ± 0·1° in a thermostat and to these

Table 2. *Dependence of oxidation rate on acidity; ionic strength* $S = 5$M.

(*a*) Lactic acid (0·186M)

$HClO_4$ (N)	h_0	k (10^{-4} sec.$^{-1}$) Found	Calc.
0·5	12·9	2·42	2·37
1·0	28·2	3·30	3·77
1·5	47·9	5·8	5·56
2·0	69·2	7·3	7·50
2·5	100·0	10·5	10·3
3·0	138	13·8	13·8
4·0	282	25·7	26·9

Calc., $k = 1{\cdot}2 + 0{\cdot}091h_0$

(*b*) Malic acid (0·194M)

$HClO_4$ (N)	h_0	k (10^{-4} sec.$^{-1}$) Found	Calc.
0·5	12·9	3·17	3·11
1·0	28·2	4·58	4·77
1·8	60·3	8·05	8·3
2·6	105	13·5	13·1
3·4	186	21·2	21·0
3·8	246	28·3	28·5
4·6	427	51·7	48·2

Calc., $k = 1{\cdot}7 + 0{\cdot}109h_0$

(*c*) Mandelic acid (0·151M)

$HClO_4$ (N)	h_0	k (10^{-4} sec.$^{-1}$) Found	Calc.
0·5	12·9	57·0	56·9
0·7	19·0	60·8	60·6
1·0	28·2	67·5	66·2
1·4	42·7	75·5	75·1
1·8	60·3	83·3	85·8
2·2	79·4	98·2	97·5
2·6	105	109	113

Calc., $k = 49{\cdot}0 + 0{\cdot}611h_0$

Pinacol (0·125M)

$HClO_4$ (N)	h_0	k (10^{-4} sec.$^{-1}$) Found	Calc.
0·5	12·9	43·5	43·3
1·0	28·2	51·7	48·1
1·8	60·3	55·7	56·2
2·6	105	70·8	67·6
3·4	186	87·8	88·1
4·2	324	112	123
(5·0	589	165 ± 10	191)

Calc., $k = 41{\cdot}0 + 0{\cdot}253h_0$

was added the aqueous hydroxy-acid. The titrimetric procedure was that of Parts I and II.[5,9] The oxidations of pinacol monomethyl ether were carried out (by J. S. L.) at 50° ± 0·1° and followed spectrophotometrically, as in Part V.[6]

[9] Littler and Waters, *J.*, 1959, 3014.

In all oxidations the organic substrate was in large excess and the logarithmic plots of titre changes indicated a strict first-order decrease in vanadium(v) concentration for over 85% of the reaction: the initial concentration of vanadium(v) was 0·050N.

TABLE 3. *Oxidation of pinacol monomethyl ether* (0·111M) *at* 50°.

$HClO_4$ (N)	1·0	1·8	2·6	3·4	4·2	5·0
k (10^{-4} sec.$^{-1}$)	(1·52)	3·53	4·8	6·31	7·75	9·55
$10^4k/[H^+]$	(1·52)	1·96	1·85	1·86	1·85	1·91

Weighted mean value: $k = (1·63 \pm 0·02) \times 10^{-3} . [H_3O^+][\text{Ether}]$.

The values of h_0 cited in Table 2 were obtained from Paul and Long's review [10] and refer to mixtures of perchloric acid and sodium perchlorate of ionic strength $S = 6$. Values for $S = 5$ are not available but should be directly proportional to those given, except possibly in 5M-perchloric acid to which no sodium perchlorate had been added.

Stoicheiometry and Oxidation Products.—Lactic, malic, and mandelic acids all consumed 2 equivalents of vanadium(v) within a few hours in 2M-sulphuric acid at 25°, but the oxidation continued slowly thereafter. After a week the equivalents of vanadium(v) consumed were: lactic acid 4·75; malic acid 3·84; mandelic acid 2·60 (increasing to 2·9 after 1 month). West and Skoog [11] found that mandelic acid consumed up to 3·9 mols. of vanadium(v) at higher concentrations of sulphuric acid.

Oxidised solutions of lactic and malic acid were shown to contain acetaldehyde by isolating the latter as its dimedone derivative, m. p. and mixed m. p. 139°. After prolonged oxidation, lactic acid solutions also gave a positive chromotropic acid test for formic acid. Mandelic acid solutions, on oxidation, soon smelt of benzaldehyde; this was characterised as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°.

One of us (J. R. J.) thanks the D.S.I.R. for a Research Studentship.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, August 12th*, 1960.]

[10] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[11] West and Skoog, *Analyt. Chem.*, 1959, **31**, 583.

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127. *Pharmacodynamic Compounds. Part II.* Some Rearrangements in the Pyrrolidine–Piperidine Series.*

By E. G. BRAIN, F. P. DOYLE, and M. D. MEHTA.

Two types of rearrangement in the pyrrolidine–piperidine series are distinguished. Thermal rearrangement of 2-chloromethyl-1-methylpyrrolidine to 3-chloro-1-methylpiperidine has been extended to several esters of 2-hydroxymethyl-1-methylpyrrolidine. Replacement reactions of 3-chloro-1-methylpiperidine with nucleophilic reagents result in partial rearrangement in the reverse direction.

IT is known that 1-chloro-2-dialkylaminopropanes when in the form of free bases readily undergo rearrangement to the isomeric 2-chloro-1-dialkylaminopropanes.[1] Fuson and Zirkle [2] have similarly shown that 2-chloromethyl-1-ethylpyrrolidine hydrochloride when treated with alkali or heated above its melting point produces 3-chloro-1-ethylpiperidine or its hydrochloride, respectively.

We have now found that, although 2-chloromethyl-1-methylpyrrolidine hydrochloride (I) and 3-chloro-1-methylpiperidine hydrochloride (II) have distinct melting points, the former appears to be partially isomerised to the latter when heated above its melting point. When carefully neutralised with cold sodium hydroxide the hydrochlorides afford

* Part I, *J.*, 1958, 4458.

[1] Kerwin, Ullyot, Fuson, and Zirkle, *J. Amer. Chem. Soc.*, 1947, **69**, 296; Brode and Hill, *ibid.*, 1947, **69**, 724; Schultz and Sprague, *ibid.*, 1948, **70**, 48.
[2] Fuson and Zirkle, *J. Amer. Chem. Soc.*, 1948, **70**, 2750.

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distinct bases without isomerisation; these were purified by low-temperature distillation and characterised as picrates and by infrared spectra.

2-Chloromethyl-1-methylpyrrolidine (III) when heated for 1 hr. at 100° was converted into 3-chloro-1-methylpiperidine (IV) to the extent of ~60%, as determined by infrared absorption measurements, a solid by-product also being formed. The recovery of the chloropiperidine (IV) unchanged after heating under the same conditions showed that this rearrangement was not an equilibration.

When the chloropyrrolidine (III) had been refluxed in propan-2-ol for 4 hr. only the chloropiperidine (IV) could be isolated. These conditions are those normally used in the Hörenstein–Pählicke method for the synthesis of esters from amino-alcohols and suggested to us that the preparation of esters from the chloride (III) by this method might lead to a mixture of pyrrolidine and piperidine derivatives. Blicke and Lu [3] reported the preparation of the benzilic ester [VI; R = $Ph_2C(OH)\cdot CO$] by this method, but by fractional crystallisation we have now found that the material obtained by following their procedure was a mixture of the pyrrolidine ester [VI; R = $Ph_2C(OH)\cdot CO$] and the piperidine ester [VII; R = $Ph_2C(OH)\cdot CO$]. Infrared analysis of the mixture indicated that the pyrrolidine ester predominated in the ratio of 7 : 3. [The hydroxymethylpyrrolidine (VI; R = H) used as starting material by Blicke and Lu [3] was probably obtained from L-glutamic acid and therefore optically active, whereas ours was racemic; this does not invalidate our finding].

This formation of a mixture could at first sight be explained by thermal rearrangement of (III) during the reaction. The proportion of pyrrolidine and piperidine esters present in the product would then depend on the relative rates of the thermal rearrangement and nucleophilic attack on the two isomeric chloro-compounds by the benzilate ion. However, nucleophilic replacements with both the bases (III) and (IV) probably proceed by way of the ion (V). Thus, the replacement reactions of 1-alkyl-3-chloropiperidine with certain nucleophilic reagents, for example, with amines,[4] hydrazines,[5] and cyanide ion [6] have been reported to yield only the corresponding 1-alkyl-2-pyrrolidylmethyl derivatives. In other reactions, a mixture of pyrrolidine and piperidine products resulted.[6,7] We have now found that the product from the reaction of the chloropiperidine (IV) and benzilic acid in propan-2-ol is a mixture of esters (VI) and (VII) [R = $Ph_2C(OH)\cdot CO$] in a similar ratio (7 : 3) to that obtained when the 2-chloromethylpyrrolidine (III) was used. This ratio was not significantly altered by the use of alkali benzilates in place of free benzilic acid or by other changes in reaction conditions.

Analogous reactions of the chloropiperidine (IV) in which this rearrangement might occur were also investigated. With acetate ion, the product was a mixture of the isomeric acetates in a ratio similar to that obtained in the case of the esters (VI and VII). With sodium benzyl oxide, however, rearrangement was complete and only 2-benzyloxymethyl-1-methylpyrrolidine (VI; R = CH_2Ph) was formed. Just as with 3-chloro-1-ethylpiperidine [6] the cyanide ion gave only the 2-cyanomethylpyrrolidine (VIII) the identity of which was established by conversion, through the ester (IX), into the known 2-2′-hydroxyethyl-1-methylpyrrolidine (X). The nitrile (VIII) was also shown by means of infrared spectra and preparation of the picrate to be different from an authentic sample of 3-cyano-1-methylpiperidine obtained from ethyl nicotinate.

Attack on an aziridinium ion by hydroxyl ion has been shown in the open-chain series to lead preferentially to the primary alcohol.[8] This appears to apply also to 3-chloro-1-methylpiperidine, since the only product isolated from alkaline hydrolysis was 2-hydroxymethyl-1-methylpyrrolidine.

[3] Blicke and Lu, *J. Amer. Chem. Soc.*, 1955, **77**, 29.
[4] Reitsema, *J. Amer. Chem. Soc.*, 1949, **71**, 2041; Biel, U.S.P. 2,874,163.
[5] Biel, Hoya, and Leiser, *J. Amer. Chem. Soc.*, 1959, **81**, 2527.
[6] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1958, 736.
[7] Biel, *J. Amer. Chem. Soc.*, 1955, **77**, 2250.
[8] Ross, *J. Amer. Chem. Soc.*, 1947, **69**, 2982.

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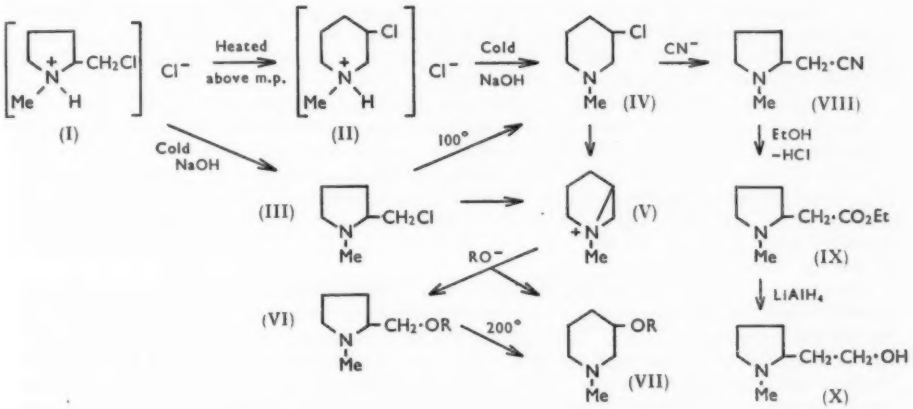
In the above nucleophilic replacement reactions the major, or sole, product was always the pyrrolidine derivative and it seemed surprising therefore that other workers had obtained mainly piperidine compounds from 1-alkyl-3-chloropiperidines by such reactions.[9,10] The possibility of thermal rearrangement of the products (possibly during isolation), as has been demonstrated for the chloro-compounds, has not hitherto been considered. This has now been shown to occur with several simple esters of 2-hydroxymethyl-1-methylpyrrolidine.

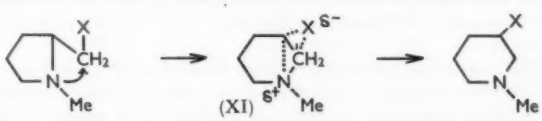
The acetate, benzoate, phenylacetate, and diphenylacetate were prepared unambiguously by the action of the appropriate acid chloride on the alcohol (VI; R = H). The corresponding esters of 3-hydroxy-1-methylpiperidine (VII; R = H) were prepared similarly for comparison.

The acetate (VI; R = Ac) was stable at 200°, but the remaining pyrrolidylmethyl esters all isomerised to some extent, as indicated by infrared measurements. The effect



of heat on 3-benzoyloxy-1-methylpiperidine (VII; R = Bz) was also investigated, but this showed none of the reverse rearrangement. Just as with the chloro-compounds (III) and (IV), therefore, the reaction is irreversible although completion is often slow.

Thermal rearrangement can thus account for the isolation of piperidine derivatives as the sole products when 3-chloropiperidines have been converted into esters,[9] since, where the ester has been isolated by distillation, it appears probable that any pyrrolidine ester formed during the initial nucleophilic reaction would revert to the piperidine isomer



by a second intramolecular thermal rearrangement during the isolation. While the nucleophilic replacement reaction is presumably ionic in character the thermal rearrangement is probably intramolecular, proceeding *via* the transition state (XI; X = halogen or acyloxy). As could be predicted, the ease of rearrangement increases with the ability of X to accommodate a negative charge in the transition state ($Cl > O{\cdot}CO{\cdot}CHPh_2 > O{\cdot}CO{\cdot}CH_2Ph > O{\cdot}CO{\cdot}CH_3$).

We have found that consideration must always be given to both types of rearrangement

[9] Cf. Biel, Friedman, Leiser, and Sprengler, *J. Amer. Chem. Soc.*, 1952, **74**, 1485; Buehler, Smith, Glenn, and Nayak, *J. Org. Chem.*, 1958, **23**, 1432.
[10] Biel, U.S.P. 2,831,862.

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in any reaction, such as the Hörenstein–Pählicke ester synthesis, involving an unsymmetrical R·CH(NR_2)·CHR'Cl grouping.

Experimental

Infrared absorption spectra were determined by Mr. K. Austin using a Grubb–Parsons double-beam spectrometer. The specimens were examined as ~3% solutions in carbon tetrachloride or in cyclohexane. Racemic compounds were used throughout this work.

3-Chloro-1-methylpiperidine.—3-Hydroxy-1-methylpiperidine [11] with an excess of thionyl chloride in chloroform gave *3-chloro-1-methylpiperidine hydrochloride* (quantitative) as needles, m. p. 187—188° after several crystallisations from dioxan–ethanol (Found: C, 42·7; H, 7·8; N, 8·0; Cl, 41·4. $C_6H_{13}Cl_2N$ requires C, 42·3; H, 7·7; N, 8·2; Cl, 41·7%). The *picrate*, prepared directly from the hydrochloride, crystallised from ethanol as pale yellow needles, m. p. 168—169° (Found: C, 40·0; H, 4·0; N, 14·8; Cl, 9·2. $C_{12}H_{15}ClN_4O_7$ requires C, 39·8; H, 4·2 N, 15·5; Cl, 9·8%).

An aqueous solution of the above hydrochloride neutralised with an excess of sodium hydroxide solution at 0° gave *3-chloro-1-methylpiperidine* (55%), b. p. 52—53°/16—17 mm., n_D^{20} 1·4677 (Found: C, 53·7; H, 9·1; N, 10·5; Cl, 26·5. $C_6H_{12}ClN$ requires C, 54·0; H, 9·1; N, 10·5; Cl, 26·6%), $\nu_{max.}$ 8·22, 11·3, 12·67, 13·18 μ.

2-Chloromethyl-1-methylpyrrolidine.—2-Hydroxymethyl-1-methylpyrrolidine [11] was converted as above into *2-chloromethyl-1-methylpyrrolidine hydrochloride* (quantitative) which after several crystallisations from dioxan–ethanol was obtained as needles, m. p. 144° (Found: C, 42·5; H, 8·2; N, 8·2; Cl, 41·6. $C_6H_{13}Cl_2N$ requires C, 42·3; H, 7·7; N, 8·2; Cl, 41·7%). The *picrate*, prepared directly from the hydrochloride, crystallised from benzene as pale yellow needles, m. p. 174—175° (mixed m. p. 159—168° with 3-chloro-1-methylpiperidine picrate described above) (Found: C, 39·7; H, 3·9; N, 15·2; Cl, 9·7. $C_{12}H_{15}ClN_4O_7$ requires C, 39·8; H, 4·2; N, 15·5; Cl, 9·8%).

An aqueous solution of this hydrochloride was carefully neutralised with aqueous sodium hydroxide, the liberated base was extracted with ether, the ether extract dried ($MgSO_4$), and the solvent removed *in vacuo*. Throughout the process of basification and extraction with ether the temperature was kept below 0°. The crude base gave a picrate, m. p. 174—175°, identical with the above picrate obtained directly from the hydrochloride. Pure *2-chloromethyl-1-methylpyrrolidine* was obtained as a liquid, b. p. below 0°/0·05 mm., n_D^{20} 1·4655 (Found: C, 54·0; H, 9·3; N, 10·5; Cl, 26·3. $C_6H_{12}ClN$ requires C, 54·0; H, 9·1; N, 10·5; Cl, 26·6%), $\nu_{max.}$ 8·26, 9·6, and 13·65 μ. The distilled base also gave a picrate, m. p. 174—175°, identical with that obtained from the hydrochloride.

Thermal Instability of 2-Chloromethyl-1-methylpyrrolidine and 3-Chloro-1-methylpiperidine.—Samples of 2-chloromethyl-1-methylpyrrolidine were heated at 100° for (*a*) 0·5 hr., and (*b*) 1 hr. The product obtained contained a little solid material; it was rapidly distilled at 0·1 mm. at room temperature. The proportion of 3-chloro-1-methylpiperidine in the total distillate estimated from the infrared absorptions at the 12·67, 13·18, and 13·65 μ bands was in (*a*) 45% and (*b*) 60%. When the chloropyrrolidine was heated at a lower temperature (50°) for 0·5 hr. no rearrangement occurred. 3-Chloro-1-methylpiperidine was unaffected when heated at 100° for 1 hr.

Instability of 2-Chloromethyl-1-methylpyrrolidine in Boiling Propan-2-ol.—A 5% solution of 2-chloromethyl-1-methylpyrrolidine in propan-2-ol was refluxed for 4 hr., cooled, acidified with concentrated hydrochloric acid, and evaporated to dryness *in vacuo*. The resulting hydrochloride was dissolved in water, and the liberated base extracted with ether, dried ($MgSO_4$), and distilled below 0° as described previously. The product (60%) had an infrared spectrum identical with that of authentic 3-chloro-1-methylpiperidine.

Acyl Derivatives of 2-Hydroxymethyl-1-methylpyrrolidine and 3-Hydroxy-1-methylpiperidine.—Authentic specimens of several acyl derivatives of 2-hydroxymethyl-1-methylpyrrolidine and 3-hydroxy-1-methylpiperidine for use as reference samples in the infrared absorption measurements and for thermal rearrangement studies were prepared. These were obtained by the reaction of the appropriate acid chloride (1 mol.) with the alcohol (1 mol.) in boiling benzene, and their properties are shown in Tables 1 and 2.

Thermal Rearrangement of Acyl Derivatives.—Samples of the acyl derivatives shown in

[11] Soulal, B.P. 820,503/1959.

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TABLE 1. *Esters (or ether) of 2-hydroxymethyl-1-methylpyrrolidine.*

No.	Acyl	Salt	M. p. or b. p./mm.	n_D^{20}	Form and solvent	Distinguishing infrared bands (μ)
1	Ac	—	74°/11	1·4454	—	8·18, 9·7
2	,,	Picrate	110—111°	—	Platelets EtOH	—
3	Bz	—	103°/0·07	1·5215	—	7·25, 7·38, 8·03
4	,,	Picrate	176—177°	—	Needles EtAc	—
5	CO·CH_2Ph	—	106°/0·2	1·5130		9·3, 10·05
6	,,	Picrate	91—92°	—	Needles EtOH	—
7	CO·$CHPh_2$	—	—	1·5545	—	7·67, 9·27, 10·1
8	,,	Picrate	106—108°	—	Needles EtOH	—
9	CO·CPh_2·OH	—	99—101° †	—	—	8·8, 10·0, 11·45, 11·56
10	(CH_2Ph ether)	—	83°/0·02	1·5144	—	*
11	(CH_2Ph ether)	Picrate	100—102°	—	Needles EtOH	—

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	61·0	9·4	9·2	$C_8H_{15}NO_2$	61·2	9·6	8·9
2	43·2	4·7	—	$C_{14}H_{18}N_4O_9$	43·5	4·7	14·5
3	71·4	7·9	6·5	$C_{13}H_{17}NO_2$	71·2	7·8	6·4
4	51·3	4·5	12·8	$C_{19}H_{20}N_4O_9$	50·9	4·5	12·5
5	71·7	8·1	6·0	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
6	52·0	4·9	11·9	$C_{20}H_{22}N_4O_9$	52·0	4·8	12·2
7	77·4	7·7	4·6	$C_{20}H_{23}NO_2$	77·7	7·5	4·5
8	58·1	4·8	10·5	$C_{26}H_{26}N_4O_9$	58·0	4·8	10·2
10	76·0	9·2	6·9	$C_{13}H_{19}NO$	76·1	9·3	6·8
11	53·6	5·0	13·3	$C_{19}H_{22}N_4O_8$	52·6	5·1	12·9

* This compound showed no bands which were absent from the piperidyl isomer (Table 2, No. 11).
† Ref. 12.

TABLE 2. *Esters (or ether) of 3-hydroxy-1-methylpiperidine.*

No.	Acyl	Salt	M. p. or b. p./mm.	n_D^{20}	Form and solvent	Distinguishing infrared bands (μ)
1	Ac	—	72°/11	1·4512	—	8·1, 8·55, 8·79, 9·4
2	,,	Picrate	122—123°	—	Needles EtOH	—
3	Bz	—	94—97°/0·05	1·5259	—	8·7, 8·8, 9·93
4	,,	Picrate	225—226°	—	Needles EtOH–EtAc	—
5	CO·CH_2Ph	—	108°/0·4	1·5151	—	9·1, 9·4, 10·23, 11·5
6	,,	Picrate	132—133°	—	Needles EtOH–EtAc	—
7	CO·$CHPh_2$	—	155—162°/0·1	1·5570	—	8·7, 9·1, 9·4, 11·5
8	,,	Picrate	128—129°	—	Needles EtOH	—
9	CO·CPh_2·OH	—	105—106° †	—	Platelets light petrol	7·4, 8·98
10	(CH_2Ph ether)	—	86°/0·2	1·5211	—	8·3, 8·55, 8·8, 9·15, 9·75
11	(CH_2Ph ether)	Picrate	114—115°		Needles EtAc	—

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	61·2	9·9	9·2	$C_8H_{15}NO_2$	61·2	9·6	8·9
2	43·7	4·9	—	$C_{14}H_{18}N_4O_9$	43·5	4·7	14·5
3	71·2	7·6	6·4	$C_{13}H_{17}NO_2$	71·2	7·8	6·4
4	50·6	4·6	12·4	$C_{19}H_{20}N_4O_9$	50·9	4·5	12·5
5	71·9	8·3	6·1	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
6	52·3	4·9	12·0	$C_{20}H_{22}N_4O_9$	52·0	4·8	12·2
7	77·5	7·8	4·8	$C_{20}H_{23}NO_2$	77·7	7·5	4·5
8	58·2	5·3	10·4	$C_{26}H_{26}N_4O_9$	58·0	4·8	10·4
9	73·9	7·2	4·2	$C_{20}H_{23}NO_3$	73·8	7·1	4·3
10	76·8	9·3	7·1	$C_{13}H_{19}NO$	76·1	9·3	6·8
11	52·9	5·1	13·1	$C_{19}H_{22}N_4O_8$	52·6	5·1	12·9

Table 1 were heated for (*a*) 1 hr. and (*b*) 5 hr. at 200° in an atmosphere of nitrogen. The total product was then distilled *in vacuo* and the mixture was analysed by infrared-absorption measurements. The compositions of the mixtures thus obtained are recorded in Table 3.

Reactions between 3-Chloro-1-methylpiperidine and Nucleophiles.—(a) *Benzilic acid.* A

[12] Doyle, Mehta, Sach, and Pearson, *J.*, 1958, 4458.

solution of 3-chloro-1-methylpiperidine (4·7 g., 1 mol.) and benzilic acid (8 g., 1 mol.) in propan-2-ol (100 ml.) was refluxed for 21 hr. and concentrated to *ca.* 30 ml. *in vacuo*. After 12 hr. at 0° the hydrochloride (8·1 g., 64%), m. p. 184—189°, that had separated was filtered off; it was dissolved in a small amount of water and the solution made alkaline with aqueous sodium

TABLE 3. *Composition * of the mixture formed by heating the esters* (VI) *at* 200°.

R	Time of heating (hr.)	Product (%) VII	VI	R	Time of heating (hr.)	Product (%) VII	VI
Ac	5	0	100	$CO{\cdot}CH_2Ph$	1	36	64
					5	69	31
Bz	1	68	32				
	5	84	16	$CO{\cdot}CHPh_2$	1	69	31
					5	91	9

* The composition was determined by infrared absorption measurement; for the acetate and benzoate at 8·8 μ, and for the phenylacetate and diphenylacetate at 9·4 μ.

hydroxide. The liberated oily base was extracted with ether, dried ($MgSO_4$), and recovered *in vacuo* as a gum (7 g.) which gave 2-(αα-diphenylglycolloyloxymethyl)-1-methylpyrrolidine as needles from heptane (m. p. and mixed [13] m. p. 105—106°). The infrared spectrum of the original gum in the 8·8 μ region indicated that it was a mixture of the pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

The heptane liquors from the crystallisation were then evaporated to a gum which on treatment with methanolic hydrogen chloride yielded a crystalline hydrochloride. This with aqueous sodium hydroxide was converted into 3-(αα-diphenylglycolloyloxy)-1-methylpiperidine, m. p. and mixed m. p. 99—101° (from heptane). A mixture of the isomeric products melted at 86—95°.

When this experiment was repeated with 2-chloromethyl-1-methylpyrrolidine instead of the chloropiperidine the resulting low-melting solid (89% yield) was found to contain the pyrrolidyl and piperidyl esters in the ratio of 3 : 2.

(b) *Sodium benzilate in propan-2-ol.* The previous experiment was repeated with sodium benzilate (8·8 g., 1 mol.) in place of the free acid. After 6 hours' refluxing the sodium chloride was separated and the filtrate evaporated to dryness *in vacuo*. The low-melting residue was triturated with dry ether and filtered to remove traces of inorganic material, and the solvent together with unchanged chloropiperidine were evaporated at 100° (bath)/0·05 mm.; the low-melting product (10·2 g., 89%) was found by infrared measurement to be a mixture of the previously described pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

(c) *Sodium benzilate in ethanol.* A solution of sodium benzilate (7·5 g., 1 mol.) in dry ethanol (50 ml.) was added during 4 hr. to a stirred boiling solution of the chloropiperidine (4·8 g., 1·2 mol.) in dry ethanol (50 ml.). Then the mixture was refluxed for 4 hr. and treated as described in experiment (b), to give a low-melting product found by infrared measurement to contain the pyrrolidyl and piperidyl esters in the ratio of *ca.* 3 : 2.

(d) *As* (c), *but inverse addition.* A solution of the chloropiperidine (4 g., 1 mol.) in ethanol (50 ml.) was slowly added to a boiling solution of sodium benzilate (9 g., 1·2 mol.) in ethanol (50 ml.). The product was found to be a mixture of pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

(e) *Sodium acetate.* A solution of 3-chloro-1-methylpiperidine (26·7 g., 1 mol.) and anhydrous sodium acetate (17 g., 1 mol.) in dry propan-2-ol (50 ml.) was refluxed for 6 hr. and then cooled. Isolation as before gave a liquid (26·4 g., 84%), b. p. 74—76°/11 mm., n_D^{20} 1·4473. The infrared absorption at 8·79 μ showed this to be a mixture of 2-acetoxymethyl-1-methylpyrrolidine and 3-acetoxy-1-methylpiperidine in the ratio of 3 : 1.

(f) *Sodium benzyl oxide.* Sodium (0·7 g., 1 atomic equiv.) was dissolved in benzyl alcohol (30 ml.) and, after the solution had been cooled to 30°, 3-chloro-1-methylpiperidine (4 g., 1 mol.) was added. The mixture was heated for 4 hr. at 100°, cooled, and shaken with 5N-hydrochloric acid (70 ml.) and ether (70 ml.). The acid extract was made alkaline with aqueous sodium hydroxide, the liberated base extracted into ether and dried ($MgSO_4$), and the solvent evaporated. The residual oil on distillation *in vacuo* gave 2-*benzyloxymethyl*-1-*methylpyrrolidine* (3·6 g., 53%), b. p. 74°/0·06 mm., n_D^{20} 1·5156. The picrate was undepressed in m. p. (99—

101°) by authentic *2-benzyloxymethyl-1-methylpyrrolidine picrate* and their infrared spectra were identical.

Authentic samples of *2-benzyloxymethyl-1-methylpyrrolidine* and *3-benzyloxy-1-methylpiperidine* required as reference compounds were obtained by the method of Paul and Tchelitcheff [6] and their properties are recorded in Tables 1 and 2.

(g) *Sodium cyanide.* The procedure of Paul and Tchelitcheff [6] was followed to give *2-cyanomethyl-1-methylpyrrolidine* (61%), b. p. 92—96°/17 mm., n_D^{20} 1·4622, $\nu_{max.}$ 7·36, 8·25, 9·55, and 10·15 μ. The *picrate* crystallised from 90% aqueous ethanol as yellow needles, m. p. 182—183° (Found: C, 43·9; H, 4·6; N, 20·2. $C_{13}H_{15}N_5O_7$ requires C, 44·2; H, 4·3; N, 19·8%). The mixed m. p. with 3-cyano-1-methylpiperidine picrate (see below) was 167—171°.

(h) *Sodium hydroxide.* The 3-chloro-1-methylpiperidine was refluxed with an excess of 10% aqueous sodium hydroxide for 2 hr. After cooling, the mixture was extracted with ether, the extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled, to give 2-hydroxy-1-methylpyrolidine (31%), b. p. 74—77°/18 mm. (picrate, m. p. and mixed m. p. 169—173°).

3-Cyano-1-methylpiperidine.[13]—Ethyl 1-methylpiperidine-3-carboxylate [14] was converted into 1-methylpiperidine-3-carboxyamide with concentrated aqueous ammonia. The crude amide was then refluxed with thionyl chloride for 3 hr. and after removal of the excess of thionyl chloride the residual 3-cyano-1-methylpiperidine was obtained as a liquid, b. p. 86°/10 mm., $\nu_{max.}$ 7·27, 8·33, 9·17, and 11·82 μ. The *picrate* crystallised from acetic acid as yellow needles, m. p. 186—187° (Found: C, 44·2; H, 4·6; N, 19·9. $C_{13}H_{15}N_5O_7$ requires C, 44·2; H, 4·3; N, 19·8%).

2-2′-Hydroxyethyl-1-methylpyrrolidine.—2-Cyanomethyl-1-methylpyrrolidine was converted by ethanolic hydrogen chloride into *ethyl 1-methyl-2-pyrrolidylacetate* (62%), b. p. 94—97°/17—18 mm., n_D^{20} 1·4484. This on reduction with lithium aluminium hydride in ether gave *2-2′-hydroxyethyl-1-methylpyrrolidine* (68%), b. p. 74°/1·5 mm., n_D^{20} 1·4735. The infrared spectrum of this alcohol was identical with that of an authentic specimen.[12] The tri-iodophenylurethane had m. p. and mixed m. p. 177° (decomp.).

The authors thank the late Sir Ian Heilbron, F.R.S., and Dr. A. H. Cook, F.R.S., for their interest, Dr. H. D. C. Rapson for discussions concerning the infrared measurements, Mr. D. Tidy for help in the experimental work, and the staff of the Micro-analytical Department.

Organic Department, Beecham Research Laboratories Ltd.,
Brockham Park, Betchworth, Surrey. [*Received, August 24th,* 1960.]

[13] Schenker and Druey, *Helv. Chim. Acta*, 1959, **42**, 1960.
[14] Feldkamp, *J. Amer. Chem. Soc.*, 1952, **74**, 3831.

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128. *A Convenient Method for the Preparation of* [^{36}Cl]*Chlorine from* [^{36}Cl]*Hydrochloric Acid: Decomposition of Palladous* [^{36}Cl]*Chloride.*

By I. C. McNeill.

Quantitative yields of chlorine may be obtained by thermal decomposition of palladous chloride *in vacuo*. [^{36}Cl]Chlorine is conveniently obtained in a vacuum system if the palladous chloride is labelled by exchange with [^{36}Cl]hydrochloric acid before decomposition. The specific activity of the chlorine obtained is shown to be the same as that expected from the initial proportions of palladous chloride and [^{36}Cl]hydrochloric acid selected.

The familiar laboratory methods for the preparation of chlorine have serious disadvantages when very small amounts of the pure gas, labelled with chlorine-36, are required for introduction into a vacuum-system. Most procedures involve oxidation of hydrochloric acid, a proportion of the original chlorine being converted into a metal chloride, and the chlorine obtained usually contains some hydrogen chloride and water as impurities. Brown, Gillies, and Stevens [1] prepared [^{36}Cl]chlorine by heating potassium peroxosulphate

[1] Brown, Gillies, and Stevens, *Canad. J. Chem.*, 1953, **31**, 768.

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with dilute aqueous [^{36}Cl]hydrochloric acid, the chlorine being swept from the solution in a stream of argon or helium. While this method overcomes some of the difficulties, the chlorine obtained may contain oxygen as an impurity, and its quantitative introduction into a vacuum-system would involve some problems.

It has been reported [2] that palladous chloride decomposes into palladium and chlorine at $\sim 600°$. Experiments carried out to test whether the decomposition occurs quantitatively show (Table 1) that when the chlorine is efficiently removed by condensation at liquid-air temperature the decomposition *in vacuo* proceeds in 99% yield. Labelled

TABLE 1.

Wt. of palladous chloride (mg.)	191·2	161·4
Wt. of chlorine (mg.)	76·3	64·4
Wt. of chlorine recovered (mg.) (%)	75·2 (98·6%)	63·7 (98·9%)

chlorine is readily obtained by dissolution of palladous chloride in aqueous [^{36}Cl]hydrochloric acid to allow exchange of chlorine, careful distillation to dryness of the solution to remove aqueous hydrochloric acid, and subsequent decomposition of the palladous [^{36}Cl]chloride *in vacuo*. It has been established that 97—99% of the chlorine based on the original weight of palladous chloride can be recovered when this procedure is followed. The only by-product is pure aqueous [^{36}Cl]hydrochloric acid of lower specific activity which can be used again.

Auric and platinic chloride also decompose to the metal and chlorine on being heated and have been used to provide a convenient source of a known amount of pure chlorine in an evacuated system.[3] The use of these chlorides in the above procedure is not feasible, however, because of decomposition of the halide during the removal of the hydrochloric acid.

A series of experiments was carried out with various ratios of unlabelled palladous chloride to [^{36}Cl]hydrochloric acid. The specific activity of chlorine resulting could be calculated on the basis of dilution of the original [^{36}Cl]hydrochloric acid activity by known amounts, with complete exchange assumed. The chlorine from each decomposition was recovered and counts of solutions of known concentration were made. Comparison of these figures with the expected values (Table 2) shows that agreement is good. The fact that the observed values tend to be slightly higher than the calculated values probably indicates the presence in the [^{36}Cl]chlorine of a small amount of hydrogen [^{36}Cl]chloride.

TABLE 2.

	Stock HCl	A	B	C	D
Unlabelled Cl (as $PdCl_2$) (mg.)		9·90	8·26	8·26	7·31
Labelled Cl (as HCl) (mg.)		9·95	11·77	14·49	27·13
Specific activity of mixture (% of original)	100	50·1	58·8	63·7	78·8
Observed counts per min. per mg. of Cl *	4550	2290	2762	2810	3710
Chemical yield (%)		98·6	97·2	92·6	98·7
Observed counts per min. per mg. of Cl, corr. for chemical yield		2320	2842	3033	3758
Calc. counts per min. per mg. of Cl	(4550)	2279	2678	2900	3585

* The mg. of chlorine present being calculated on the assumption of 100% yield from the palladous chloride decomposition.

These experiments show that labelling of palladous chloride by exchange with [^{36}Cl]-hydrochloric acid and subsequent decomposition of the [^{36}Cl]palladous chloride provides a convenient and reliable method by which [^{36}Cl]chlorine, in known amount and of known specific activity, may be obtained in an evacuated system.

[2] Puche, *Compt. rend.*, 1935, **200**, 1206.
[3] Travers, "Experimental Study of Gases," Macmillan and Co., New York, 1901, p. 47.

The analogous thermal decomposition of labelled palladous iodide has been used previously in these laboratories [4] as a convenient method for the preparation of labelled iodine.

Experimental

Decomposition of Unlabelled Palladous Chloride.—Palladous chloride (Johnson, Matthey and Co. Ltd.) was dried at 100° for 24 hr. and stored in a desiccator. Samples were weighed into 50 ml. Pyrex distillation flasks, and the necks of the flasks were sealed off above the side arms. Each flask was then fused on to a receiving vessel containing an excess of 0·1M-potassium iodide, this vessel being attached to a high-vacuum system. Greased joints or taps between decomposition flask and receiver were avoided since chlorine attacks tap-grease. After the solutions had been degassed and frozen at −180° the apparatus was evacuated and sealed off beyond each receiving vessel. The palladous chloride samples were subsequently decomposed by heating them with a gas flame to a temperature just below the softening point of Pyrex glass, the chlorine being condensed in the receivers at −180°. After the receivers had been sealed off from the decomposition vessels, the potassium iodide solutions were thawed to room temperature. Reaction of the chlorine with the potassium iodide produced iodine, which dissolved in the excess of potassium iodide present. The liberated iodine, and hence the weight of chlorine collected, was estimated by titration against standard sodium thiosulphate solution. Table 1 shows the results obtained, indicating that 99% of the theoretical yield of chlorine can be recovered.

Concentration of Stock [^{36}Cl]*Hydrochloric Acid Solution.*—[^{36}Cl]Hydrochloric acid (The Radiochemical Centre, Amersham), of nominal specific activity 0·109 μc/mg., was transferred to a standard flask and made up to the graduation mark with distilled water. The chlorine content per ml. of solution was determined gravimetrically by precipitation as silver chloride. The solution contained 9·05 mg. of Cl per ml.

Decomposition of [^{36}Cl]*Palladous Chloride.*—Known volumes of the stock [^{36}Cl]hydrochloric acid solution were added to weighed amounts of palladous chloride. From the respective weights of labelled and unlabelled chlorine, the diluted activities were calculated (Table 2). The neck of each flask was washed down with distilled water before being sealed off. Samples were gently heated to dissolve the palladous chloride, then slowly (½—1 hr.) evaporated almost to dryness at atmospheric pressure. The distillate is pure [^{36}Cl]hydrochloric acid of reduced specific activity, which may be retained for future use. Care is required when the samples are nearly dry to avoid overheating, otherwise slight loss of chlorine may occur. The last traces of water and hydrogen chloride were removed in these experiments by immersing the bulbs of the flasks in an oil-bath at 120° for 4 hr. Any droplets of distillate which appeared in the side-arms were removed by means of tissue. Decomposition of the chloride and recovery of chlorine were carried out as already described. Thiosulphate titration indicated that the yields of chlorine were generally 97—99% (Table 2).

Counting of [^{36}Cl]*Chlorine Obtained.*—The active solutions, containing chlorine as chloride ion in presence of iodine and potassium iodide, were made up to a known volume with distilled water, and the activity of 10-ml. portions was determined by normal technique (halogen quenched liquid counter tube). Dilutions of the stock [^{36}Cl]hydrochloric acid solution (in presence of the same concentration of potassium iodide) were counted under similar conditions. Values of counts per minute per mg. of chlorine for each sample (corrected for the small amounts of chlorine not recovered) were then compared with the values already calculated for the samples on the basis of dilution of activity. Results are given in Table 2.

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Londonderry Laboratory for Radiochemistry, University of Durham,
South Road, Durham. [*Received, August 31st,* 1960.]

[4] Purkayastha and Martin, *Canad. J. Chem.*, 1956, **34**, 293.

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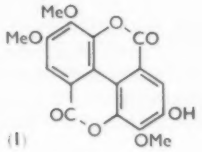
129. *Constituents of* Eugenia maire *A. Cunn. Part I. A Trimethyl Ether of Ellagic Acid and Mairin, a new Triterpene.*

By Lindsay H. Briggs, R. C. Cambie, J. B. Lowry, and R. N. Seelye.

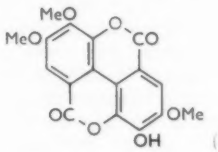
A new, naturally occurring, trimethyl ether of ellagic acid, β-sitosterol, and mairin, a new dihydroxytriterpene, have been isolated from the trunk bark of *Eugenia maire* A. Cunn. The ether has been identified as 3,3′,4-tri-*O*-methylellagic acid (I).

Eugenia maire A. Cunn. (Maori name, " Maire-tawake "; Fam. Myrtaceae) is a tree found in the lowland forests of New Zealand where it is endemic and the only member of the genus in the country. By extraction of the trunk bark with methanol a sparingly soluble phenol, m. p. 293—294°, was isolated in 0·64% yield. It was also isolated in lower yield (0·03%) from the trunk wood but was absent in both the root bark and wood. Analyses, determination of equivalent weight by potentiometric titration, and solubility in aqueous sodium carbonate agreed for a compound, $C_{17}H_{12}O_8$, possessing three methoxyl groups and an activated phenolic group but no carboxylic acid function. It formed a monoacetate, a monobenzoate, and a monomethyl ether, each of which was insoluble in cold alkali and showed no hydroxyl absorption in the infrared spectra. The absence of normal carboxyl or ester groups was shown by recovery of the phenol after attempted formation of ketonic derivatives and after prolonged treatment with alkali under mild conditions in the absence of oxygen. The presence of an αβ-unsaturated lactone was shown by a strong carbonyl band [1] at 1754 cm.$^{-1}$. In potentiometric titrations, however, the compound did not behave as a typical lactone and its similarity in this respect,[2-4] its ultraviolet spectrum, and its other properties [4] suggested a close relationship to ellagic acid.

The identification of its methyl ether as tetra-*O*-methylellagic acid showed that it was a trimethyl ether of ellagic acid, and this was confirmed by mild demethylation with concentrated sulphuric acid to give ellagic acid. Only two structures (I and II)



(I)



(II)

are possible for the trimethyl ether and, at the beginning of the investigation there was no record of it in the literature. Distinction between the structures was possible from the expected ionic behaviour of the free hydroxyl group in each case. The 3,3′-hydroxyl groups of ellagic acid have greater acidity than those in the 4,4′-positions,[2,4,5] and Jurd has shown it is possible to ionise, selectively, the two pairs of hydroxyl groups by the use of bases of varying strength, thus obtaining characteristic shifts of the absorption peaks of the ultraviolet spectrum. When the 3,3′-hydroxyl groups only are free a change of the short-wavelength peak occurs in the presence of sodium acetate. Ionisation of the 4,4′-hydroxyl groups, however, requiring a stronger base, occurs in the presence of sodium ethoxide which causes a bathochromic shift of the long-wavelength band. The spectrum of our phenol was unchanged in the presence of sodium acetate, strongly suggesting that

[1] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn. 1958, p. 178.
[2] Schweitzer, *Collegium*, 1933, 149; *Chem. Abs.*, 1933, **27**, 3107.
[3] Sunthankar and Jatkar, *J. Indian Inst. Sci.*, 1938, **21**, *A*, 189.
[4] Hathway, *Nature*, 1956, **177**, 747.
[5] Jurd, *Chem. and Ind.*, 1959, 261; *J. Amer. Chem. Soc.*, 1959, **81**, 4610.

the free hydroxyl group was in the 4-position, as in (I). It was desirable, however, to distinguish between the possible structures by unequivocal synthesis.

During the investigation in this direction Jurd [6] prepared 3,3',4-tri-*O*-methylellagic acid (I) by an unambiguous synthesis. The recorded melting points for this compound (283°) and its acetate (251°) differed somewhat from those of our product (293—294°) and its acetate (264—265°), although spectral shifts [7] were identical for both compounds. 4-*O*-Acetyl-3,3',4-tri-*O*-methylellagic acid prepared by us by Jurd's method had, however, a melting point of 264°, identical with that of our acetate while a mixed-melting-point determination and comparison of the infrared spectra proved the identity. Deacetylation of the synthetic product led to 3,3',4-tri-*O*-methylellagic acid, m. p. 293—294°, identical with the natural phenol. Further, samples of 3,3',4-tri-*O*-methylellagic acid and its acetate kindly supplied by Dr. L. Jurd, possessed infrared spectra identical with those of the natural product and its acetate, respectively.

Bate-Smith has shown [8] that ellagic acid occurs in 42 families belonging to 15 of the 40 orders of dicotyledonous plants. The family Myrtaceae belongs to the group (Myrtiflorae) which exhibits the most systematic distribution, ellagic acid being found in all families and most of the species, where it is usually associated with myricetin and leucodelphinidin. Unexpectedly, neither of these two compounds was detected in the wood and bark of *Eugenia maire* when extracts were examined chromatographically,[4,8] nor was ellagic acid.

After separation of this phenol, β-sitosterol and a new triterpene, mairin, $C_{30}H_{48}O_3$, m. p. 295—296°, were isolated from the trunk-bark extract. Mairin is neutral and forms a diacetate and a dibenzoate, each of which shows no hydroxyl absorption in its infrared spectrum. It contains no carbonyl group so that the remaining oxygen atom must be present as an ether. Further structural work is in progress.

Experimental

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infrared spectra were measured for KBr discs with a Beckman IR2 instrument, and ultraviolet spectra for EtOH solutions with a Beckman DU instrument. Ultraviolet spectral shifts were measured by the method of Jurd and Horowitz.[9] Optical rotations were measured for $CHCl_3$ solutions, unless otherwise stated.

3,3,4-*Tri*-O-*methylellagic Acid* (*Natural*).—Ground, air-dried trunk bark (7·1 kg.) of *Eugenia maire* A. Cunn. was extracted (Soxhlet) in batches with methanol for 100—120 hr., fresh solvent being used after 40 hours' extraction. Separation of deposited solid from the initial extracts and from the concentrated mother-liquors gave crude *product*. That obtained from the second extract was less contaminated and was worked up separately. Repeated crystallization from ethylene glycol and then from dioxan gave colourless needles (total yield 46 g.), m. p. 293—294°, with slow sublimation from 288° [Found (sample crystallized from dimethylformamide): C, 59·25; H, 4·0; (sample crystallized * from ethylene glycol): C, 58·9; H, 4·0; OMe, 21·4; (sample crystallized * from dioxan; dried at 100°): C, 59·0, 59·4; H, 3·5, 3·2; OMe, 24·9, 25·4; (sample crystallized * from dioxan; dried at 150°): C, 59·2, 59·3, 59·0; H, 3·35, 3·5, 3·6; OMe, 25·4, 25·1. $C_{17}H_{12}O_8$ requires C, 59·3; H, 3·5; 3OMe, 27·5%],† $\lambda_{max.}$ 249 (log ε 4·64), 355 (sh), and 370 mμ (log ε 4·07), $\nu_{max.}$ 3436 (OH), 2985, 2899, 1462, 1359, 1245, 1175, 1129 (OMe [10]),

* For analysis samples were crystallized four times.

† In methylated ellagic acid and hexahydrobiphenic acid derivatives normal Zeisel determination has been found to give low results; this has been attributed to incomplete removal of methoxyl groups (Herzig and Pollak, *Monatsh.*, 1908, **29**, 263; Mayer, *Z. analyt. Chem.*, 1954, **141**, 345). Since our trimethylellagic acid is readily demethylated by concentrated sulphuric acid, incomplete removal of methoxyl groups is probably due to the observed insolubility rather than to stability of the O–methyl bond.

[6] Jurd, *J. Amer. Chem. Soc.*, 1959, **81**, 4606.
[7] Jurd, Palmer, Stitt, and Shoolery, *J. Amer. Chem. Soc.*, 1959, **81**, 4620.
[8] Bate-Smith, *Chem. and Ind. B.I.F. Review*, 1956, R32.
[9] Jurd and Horowitz, *J. Org. Chem.*, 1957, **22**, 1618; see also refs. 5 and 7.
[10] Briggs, Colebrook, Fales, and Wildman, *Analyt. Chem.*, 1957, **29**, 904.

XUM

1754 (lactone CO) cm.$^{-1}$. The single lactone peak and the lower frequency than that of ellagic acid (1695 cm.$^{-1}$) are in accord with the findings of Stitt, Gong, Palmer, and Schoolery [10a] for substituted ellagic acids.

Rapid potentiomeric titrations of a purified dioxan solution with 0·083N-aqueous potassium hydroxide, in an atmosphere of nitrogen, gave an equiv. wt. of 341 (average of five determinations ($C_{17}H_{12}O_8$ requires *M*, 344). Potentiometric back-titration in an atmosphere of nitrogen, with 0·062N-aqueous hydrogen chloride gave an equivalent weight of 340 (average of four determinations). In common with ellagic acid and its derivatives, trimethylellagic acid yields yellow solutions in alkali and, reacting in a tautomeric quinonoid form,[4] can be oxidised by air, resulting in further hydroxylation and intermolecular linking.[11] For this reason accurate results in potentiometric titrations can only be obtained by the exclusion of oxygen.

The freshly purified phenol became a very pale yellow on exposure to light and air. It is slowly soluble in methanol, ethanol, and acetone but freely soluble in pyridine, butan-1-ol, cyclohexanol, and phenol. It is insoluble in camphor (Rast) or camphorquinone. In pyridine solution it gives a brown colour with alcoholic ferric chloride.

Extraction of the ground aerial wood of *Eugenia maire* (200 g.) and working up of the methanol-insoluble portion of the extract gave the same material (60 mg.), m. p. and mixed m. p. 293—294° (identical infrared spectrum).

Acetylation with acetic anhydride–pyridine (100° for 8 hr. or 115° for 3 hr.; after shorter periods reaction was incomplete), acetic anhydride–sulphuric acid (100°, 1 hr.), or acetic anhydride–perchloric acid (room temp., ½ hr.) yielded a *monoacetate* which crystallized from dioxan or acetic anhydride as colourless needles, m. p. 264—265° (Found: C, 58·9, 59·2; H, 3·4, 3·6; OMe, 23·4; Ac, 12·6. $C_{19}H_{14}O_9$ requires C, 59·1; H, 3·65; 3OMe, 24·0; Ac, 11·15%), $\lambda_{max.}$ 248 (log ε 4·48), 344 (log ε 3·88), and 357 mμ (log ε 3·90), $\nu_{max.}$ 1736 (lactone CO), 1770 (acetyl CO) cm.$^{-1}$.

With benzoyl chloride–pyridine (100°, 2½ hr.) it gave an oil which after trituration with ether and crystallization from aqueous dioxan gave a *monobenzoate*, colourless needles, m. p. 254—255° (Found: C, 64·1, 64·0; H, 3·6, 3·6; Bz, 22·6. $C_{24}H_{16}O_9$ requires C, 64·3; H, 3·6; Bz, 23·5%).

Methylation. The natural product (500 mg.) in 2N-sodium hydroxide (10 c.c.) was shaken with dimethyl sulphate (1·5 c.c.) for 3 hr. at room temperature. Crystallization of the precipitated solid from ethylene glycol gave pale yellow needles (426 mg.) of the methyl ether, m. p. 341—342°. The same derivative was prepared by use of diazomethane in methanol–ether at 0° for 24 hr. (98% yield) and by prolonged heating (60 hr.) of a suspension in dry acetone with dimethyl sulphate and anhydrous potassium carbonate (95% yield). The m. p. was undepressed by a sample of tetra-*O*-methylellagic acid and the infrared spectra were identical (Found: C, 59·8, 59·7; H, 3·7, 3·75; OMe, 29·3. Calc. for $C_{18}H_{14}O_8$: C, 60·3; H, 3·9; 4OMe, 34·6%).

Demethylation. The natural product (500 mg.) was heated under reflux with concentrated sulphuric acid (10 c.c.) at 140° for 10 min. and the cooled solution poured into water. Crystallization of the flocculent precipitate from dimethylformamide gave a solvate of ellagic acid (410 mg.) as pale yellow needles, m. p. >360° [Found: C, 53·65; H, 4·5; OMe, 0. Calc. for $C_{14}H_6O_8(C_3H_7ON)_2$: C, 53·6; H, 5·0%], $\lambda_{max.}$ 255 (log ε 4·64), 352 (sh), and 366 mμ (log ε 4·03). The infrared spectrum was identical with that of an authentic sample crystallized from the same solvent. Acetylation with acetic anhydride–anhydrous sodium acetate (100°, ½ hr.) gave the tetra-acetate which crystallized as needles, m. p. and mixed m. p. 341—343° (Found: C, 56·2; H, 3·3. Calc. for $C_{22}H_{14}O_{12}$: C, 56·2; H, 3·0%). The retention of solvent is usual and has received notice by a number of workers.[12]

3,3′,4-Tri-O-methylellagic Acid Monoacetate.—Ellagic acid tetra-acetate was converted into ellagic acid diacetate, pale yellow needles, m. p. 327—330° (lit.,[6] m. p. 325—327°), by Jurd's method.[6] Methylation of a dry acetone suspension of the diacetate (2·0 g.) with dimethyl sulphate (4 c.c.) and anhydrous potassium carbonate (3·0 g.) for 3 hr. and working up by Jurd's method gave 4,4′-di-*O*-acetyl-3,3′-di-*O*-methylellagic acid (1·4 g.), m. p. 302—304° (lit.,[6] m. p. 304—305°), and, from the acetone solution, 4-*O*-acetyl-3,3′,4′-tri-*O*-methylellagic acid (120 mg.),

[10a] Stitt, Gong, Palmer, and Schoolery, *J. Amer. Chem. Soc.*, 1959, **81**, 4615.
[11] Feist and Bestehorn, *Arch. Pharm.*, 1925, **263**, 16.
[12] Goldschmidt, *Monatsh.*, 1905, **26**, 1139; Kunz-Krause, *Arch. Pharm.*, 1921, **259**, 193; Zetzsche and Graef, *Helv. Chim. Acta*, 1931, **14**, 240; Cambie, *New Zealand J. Sci.*, 1959, **2**, 257).

XUM

needles (from dioxan), m. p. 263—264°. The m. p. was undepressed on admixture with a sample prepared by Dr. L. Jurd (m. p. 251°) or by the acetate of the natural product (identical infrared spectra) (Found: C, 59·4; H, 3·7; Ac, 11·6. Calc. for $C_{19}H_{14}O_9$: C, 59·1; H, 3·65; Ac, 11·15%).

3,3′,4-Tri-O-methylellagic Acid (Synthetic).—Treatment of a suspension of the monoacetate (80 mg.) in 50% aqueous methanol (10 c.c.) with 5% aqueous potassium hydroxide (5 c.c.) by Jurd's method [6] gave 3,3′,4-tri-*O*-methylellagic acid (30 mg.), colourless needles, m. p. 293—294° after repeated crystallization from dioxan. The m. p. was undepressed on admixture with a sample prepared by Dr. L. Jurd (m. p. 283°) or by the natural product (identical infrared spectra).

β-*Sitosterol.*—The methanolic mother-liquors from the initial extract of the bark were reduced in volume, yielding a coloured solid and finally a black tar. The solid was extracted with benzene, leaving further tri-*O*-methylellagic acid as an insoluble residue, and the extract was chromatographed on activated alumina (P. Spence & Co., grade H). Crystallization from aqueous methanol of fractions eluted from the column with benzene gave plates of β-sitosterol (100 mg.), m. p. 135—136° (Found: C, 82·4; H, 12·4. Calc. for $C_{29}H_{50}O,\frac{1}{2}H_2O$: C, 82·2; H, 12·1%). The acetate, prepared by the use of acetic anhydride–pyridine (100°, 30 min.), had m. p. and mixed m. p. 124—125° (identical infrared spectra). Extraction of the black tar with ether and chromatography of the extract in benzene on alumina yielded further β-sitosterol (20 mg.).

Mairin.—The remaining tar was extracted repeatedly with cold 10% aqueous sodium carbonate which separated ellagitannins.[13] The alkali-insoluble residue, after repeated crystallization from methanol (charcoal) and separation from waxes was comprised mainly of long-chain esters, yielded long colourless needles, of *mairin* (5·0 g.), m. p. 295—296°, with sintering from 285°, $[\alpha]_D^{23}$ +10·6° (*c* 0·71), +10·65° (*c* 1·85 in pyridine) [Found: C, 77·2; H, 10·1. $C_{30}H_{48}O_3,\frac{1}{2}CH_3{\cdot}OH$ requires C, 77·3; H, 10·7. Found (for sample dried to constant wt.): C, 79·3; H, 10·5%; *M* (Rast), 453, 464. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%; *M*, 457], $\nu_{max.}$ 3584 (OH), 3472 (OH), 2959 (CH_3) cm.$^{-1}$.

Mairin gave a violet colour in the Liebermann–Burchard reaction but negative Zimmermann, Salkowski, and Rosenheim tests. It gave no colour with tetranitromethane, did not decolorize dilute potassium permanganate or bromine in chloroform, and was recovered after being heated under reflux with methanolic potassium hydroxide for 1 hr.

Mairin (150 mg.) with acetic anhydide–pyridine (100°, 1 hr.) gave a *diacetate* (110 mg.) which crystallized from aqueous methanol as thick plates, m. p. 289—290°, $[\alpha]_D^{23}$ +25·2 (*c* 1·11) (Found: C, 75·5; H, 9·7. $C_{34}H_{52}O_5$ requires C, 75·7; H, 9·2%).

Mairin (200 mg.) with benzoyl chloride–pyridine (100°, 1 hr.) gave an oil which was triturated with aqueous sodium hydrogen carbonate and then with light petroleum to yield a crystalline *dibenzoate*. Recrystallization from aqueous methanol–dioxan gave prisms (190 mg.), m. p. 331—333°, $[\alpha]_D^{23}$ +45·4° (*c* 1·24) (Found: C, 78·9, 78·2; H, 9·5, 8·9. $C_{42}H_{56}O_5$ requires C, 78·7; H, 8·8%).

We are indebted to Dr. L. Jurd for samples of 3,3′,4-tri-*O*-methylellagic acid and its acetate and to Dr. R. C. Cooper for identification and assistance in the collection of *Eugenia maire* samples. Assistance is gratefully acknowledged from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, and the Research Grants Committee of the University of New Zealand.

Department of Chemistry,
University of Auckland, New Zealand. [*Received, July 4th*, 1960.]

[13] Ware, *Analyst*, 1925, **50**, 384.

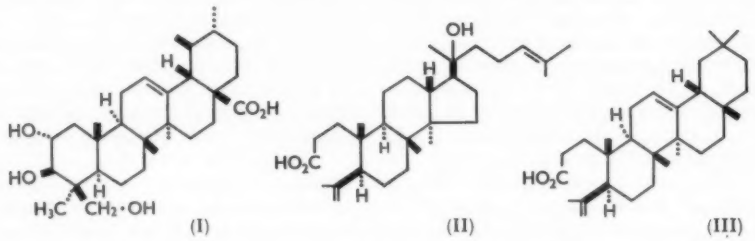
XUM

130. *The Chemistry of Triterpenes and Related Compounds. Part XXXVIII.* The Acidic Constituents of Dammar Resin.*

By S. Brewis and T. G. Halsall.

The acidic constituents of dammar resin have been further investigated. The so-called dammarolic acid has been shown to be asiatic acid (I). Two new triterpene acids which do not contain a hydroxyl or keto-group have been isolated as their methyl esters. Some reactions of the known constituent dammarenolic acid are described.

Recently we have been concerned [1] with hydroxyhopanone, a neutral constituent of dammar resin, and have also been interested in the acidic constituents of the resin. Mills and Werner [2] have already investigated the acids in some detail and isolated ursonic, dammarolic, dammarenolic, and dammarenonic acid as their methyl esters. Only the first of these was an acid of known structure. The crude acids from dammar resin have now been further investigated, Mills and Werner's procedure being followed. While the work was in progress the structure of dammarenolic acid was elucidated [3] as (II), and only a few additional experiments on the acid are described later in this paper.



(I) (II) (III)

Dammarolic acid, m. p. 325—326°, was first isolated from the resin by Mladenovic and Barkovic [4] who considered it to be a saturated monobasic acid, $C_{30}H_{50}O_6$, with four hydroxyl groups, of which one was primary and one secondary. Mills and Werner,[2] by repeated recrystallisation of the ether-insoluble acidic fraction of the resin, obtained an acid, m. p. *ca.* 315°, which appeared identical with dammarolic acid. It was characterised as its methyl ester, m. p. 222—224°, $[\alpha]_D$ +52°, which gave a yellow colour with tetranitromethane and gave analytical results in agreement with $C_{31}H_{50\text{-}52}O_6$.

In our investigation the ether-insoluble portion of the acidic fraction of dammar resin was methylated with diazomethane, and the resulting methyl esters were separated by chromatography on alumina. The following compounds were isolated, in order of elution: methyl ursonate, " compound A " (m. p. 147—149°, $[\alpha]_D$ +48°), methyl dammarenolate, " compound B " (m. p. 234—236°, $[\alpha]_D$ +117°), and methyl dammarolate (m. p. 223—225°, $[\alpha]_D$ +50°).

Methyl dammarolate proved to be difficult to analyse (cf. Mills and Werner [2]), but the analytical data indicated the formula $C_{31}H_{50}O_5$ rather than $C_{31}H_{50\text{-}52}O_6$ as previously suggested. Its ultraviolet spectrum showed " end-absorption " typical of a trisubstituted double bond. Boiling ethylene glycol had to be used as the solvent for the hydrolysis of the ester as it was recovered unchanged from boiling methanolic potassium hydroxide.

* Part XXXVII, *J.*, 1960, 1715.

[1] Dunstan, Fazakerley, Halsall, and Jones, *Croat. Chim. Acta*, 1957, **29**, 173; Fazakerley, Halsall, and Jones, *J.*, 1959, 1877; Baddeley, Halsall, and Jones, *J.*, 1960, 1715.

[2] Mills and Werner, *J.*, 1955, 3132.

[3] Arigoni, Barton, Bernasconi, Djerassi, Mills, and Wolff, *Proc. Chem. Soc.*, 1959, 306; *J.*, 1960, 1900.

[4] Mladenovič and Barkovič, *Monatsh.*, 1940, **73**, 306.

The ester was shown to contain a 1,2-glycol group by its reaction with lead tetra-acetate. From these results and a comparison of the constants of the ester and the corresponding acid with those of methyl asiatate and asiatic acid [5] (I) it appeared likely that the two compounds were identical. This identity was confirmed by a mixed melting point determination between methyl dammarolate and methyl asiatate (kindly supplied by Professor E. Lederer), no depression being observed. The infrared spectra (in " Nujol ") of the two samples were identical. The so-called dammarolic acid is therefore asiatic acid.

	Acid		Methyl ester	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
Dammarolic acid	*ca.* 317° (decomp.)	+48°	223—225°	+50°
Asiatic acid [5]	310	+53	225	+52

" Compound A " and " compound B," isolated in low yield, are of interest as there is no spectroscopic evidence in either case for a hydroxyl or six-membered-ring keto-group so characteristic of triterpenes. The absence of these functional groups suggests that a normal triterpene ring A cannot be present in these compounds, and that the parent acids may be transformation products of normal triterpenes with ring A, at least, modified. The infrared spectra of these compounds had no band at 890 cm.$^{-1}$, so ring A cannot have been modified exactly as in dammarenolic acid [3] (II) and nyctanthic acid [6] (III).

" Compound A " gives analytical values indicative of $C_{32}H_{48-50}O_6$ or $C_{33}H_{50-52}O_6$. Its infrared spectrum with a broad band at 1727 cm^{-1} suggests that it is a dimethyl ester. Measurements of the apparent integrated absorption intensity of this band by the method of Jones, Ramsey, Keir, and Dobriner [7] are in agreement with the presence of two carbonyl groups. A strong band at 1140 cm.$^{-1}$ indicates [8] that the remaining two oxygen atoms may be present in ether linkages. The ultraviolet spectrum of " compound A " is very similar to that of methyl ursonate. " Compound A " was recovered unchanged after 24 hr. in 10% methanolic potassium hydroxide.

" Compound B " gives analytical values indicative of $C_{32}H_{50-52}O_6$ and appears to be an unsaturated dimethyl ester lactone. The infrared spectrum (in CCl_4), with bands at 1745, 1427, and 1060 cm.$^{-1}$, agrees [9] with the presence of a δ-lactone grouping. When " compound B " was treated with methanolic potassium hydroxide at room temperature for two days the product isolated after acidification contained no lactone ring. The apparent integrated absorption intensity of the carbonyl bands of the infrared spectrum of " compound B " indicated [7] the presence of three carbonyl groups, accounted for by the δ-lactone group and two methoxycarbonyl groups (band at 1730 cm.$^{-1}$). The ultraviolet absorption spectrum of " compound B " was similar to that of methyl ursonate and methyl asiatate. These results suggest that the parent acids corresponding to " compound A " and " compound B " may be derived from α-amyrin derivatives, ring A having been modified and further oxidation having occurred.

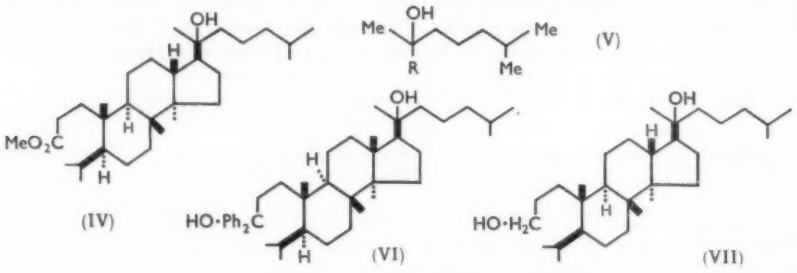
Methyl tetrahydrodammarenolate [3] (IV) was dehydrated and the product ozonised: formaldehyde and isohexanal were isolated as their 2,4-dinitrophenylhydrazones, indicating the side chain (V). The C_8 nature of the side chain was confirmed by the pyrolytic procedure of Cox, High, and Jones.[10] Treatment of the tetrahydro-ester with phenylmagnesium bromide gave a crystalline alcohol (VI) which was dehydrated to a substituted α-phenylstyrene with maximal absorption at 2525 Å (ε 17,400), indicating the chromophore $Ph_2C{=}CHR$ and hence of the grouping $-CH_2{\cdot}CO_2H$ in dammarenolic acid. Compounds

[5] Boiteau, Buzas, Lederer, and Polonsky, *Nature*, 1949, **163**, 258; Polonsky, *Bull. Soc. chim. France*, 1953, 173; Djerassi, Thomas, Livingston, and Thompson, *J. Amer. Chem. Soc.*, 1957, **79**, 5292.
[6] Whitham, *Proc. Chem. Soc.*, 1959, 271; *J.*, 1960, 2016.
[7] Jones, Ramsey, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80.
[8] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen & Co., London, 1958, p. 116.
[9] Jones and Gallagher, *J. Amer. Chem. Soc.*, 1959, **81**, 5242.
[10] Cox, High, and Jones, *Proc. Chem. Soc.*, 1958, 234.

XUM

with the grouping $Ph_2C{=}CRR'$ absorb at 2450—2480 (cf. ref. 11) and $Ph_2C{=}CHR$ at 2515—2530 Å (cf. ref. 12). Reduction of methyl tetrahydrodammarenolate (IV) with lithium aluminium hydride gave the corresponding diol (VII), characterised as its monoacetate.

Incidentally, a polymorphic form of dammarenolic acid was obtained.



Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined for chloroform solutions at room temperature. Light petroleum refers to the fraction with b. p. 60—80°. The alumina used for chromatography was Peter Spence's grade "H." Activity II refers to grade "H" alumina deactivated with 5% of 10% acetic acid, and activity III to grade "H" alumina deactivated with 10% of 10% acetic acid.

Examination of the "Ether-insoluble" Acids from Dammar Resin.—The crude acids (200 g.) obtained from dammar resin were powdered and heated under reflux with ether (2 l.). The resulting milky suspension was centrifuged, and the clear ethereal solution decanted from the gelatinous residue. The residue was dried to give an amorphous pale yellow solid (22·8 g.) which was heated under reflux in ethanol (300 c.c.). The resulting yellow solution was filtered and a portion of the filtrate (250 c.c.) was diluted with ethanol (250 c.c.) and cooled to below 5°. The cooled solution was treated overnight with an excess of ethereal diazomethane, to give a mixture of methyl esters (14 g.) which was adsorbed from benzene on alumina (activity III) (1 kg.). The alumina was eluted with benzene (2 l.), then with benzene–ether, the ether increasing in concentration by increments of 10% for every 500 c.c. of eluant, next ether alone, and finally ether containing 5% of methanol. Fractions of 500 c.c. volume were collected.

Fractions 1—4 were combined to give a pale yellow glass (2·4 g.) which was rechromatographed as described below. Fraction 5 was recrystallised from methanol, to give *compound B* (150 mg.) as spars, m. p. 228—233°, raised by further recrystallisation to 234—236°, $[\alpha]_D$ +117° (*c* 0·93) (Found: C, 72·45; H, 9·15. $C_{32}H_{50}O_6$ requires C, 72·4; H, 9·5. $C_{32}H_{52}O_6$ requires C, 72·1; H, 9·8%), $\nu_{max.}$ (in CCl_4), 1745, 1730, 1642, 1220, 1181, 1138, and 1060 cm.$^{-1}$, (in CS_2) 818 and 805 cm.$^{-1}$ (in CCl_4; spectrum determined on a "Unicam" S.P. 100 infrared spectrophotometer) 1750 (ε_a 982) and 1727 cm.$^{-1}$ (ε_a 826), $\Delta\nu_{\frac{1}{2}}^{a} = 38$ cm.$^{-1}$, $B = 8{\cdot}9 \times 10^4$ mole^{-1} l. cm.$^{-2}$.*

Fractions 6—19 yielded small amounts of resins which were not further investigated. Fraction 20 and subsequent fractions were eluted with 5% methanol in ether. Recrystallisations of these fractions from aqueous methanol yielded methyl asiatate (dammarolate) as needles (1·5 g.), m. p. 223—225°, $[\alpha]_D$ +50° (*c* 1·31) (Found: C, 73·0, 72·7; H, 9·8, 9·9; O, 16·75. Calc. for $C_{31}H_{50}O_5$,$\frac{1}{2}$MeOH: C, 72·9; H, 10·1; O, 17·0%), $\nu_{max.}$ (in "Nujol") 3448 and 1725 cm.$^{-1}$. A sample recrystallised from benzene was analysed (Found: C, 74·0; H, 10·0. Calc. for $C_{31}H_{50}O_5$: C, 74·05; H, 10·05%). The m. p.s and mixed m. p. of the methyl ester and of authentic methyl asiatate, determined simultaneously in an oil-bath, were all 215—217°. The infrared spectra of the methyl ester and methyl asiatate were identical.

Chromatography of fractions 1—4. These fractions were adsorbed from light petroleum on

* ε_a = apparent molar extinction coefficient. $\Delta\nu_{\frac{1}{2}}^{a}$ = apparent half band width. $B = \frac{M}{cl}\int_{\nu_1}^{\nu_{11}} \ln\frac{T_0}{T}\,d\nu$ where M = molecular weight, c = concn. in g./l., and l = cell width in cm.[7]

[11] Cocker and Halsall, *J.*, 1956, 4262; Turnbull, Vasistha, Wilson, and Woodger, *J.*, 1957, 569; Shoppee and Stephenson, *J.*, 1954, 2230.

[12] Cocker and Halsall, *J.*, 1956, 4262; Davy, Jones, and Halsall, *Rec. Trav. chim.*, 1950, 368.

alumina (activity III) (250 g.). The column was eluted with light petroleum (750 c.c.), followed by benzene–light petroleum, the benzene increasing in concentration by increments of 10% every 250 c.c., and finally benzene. Fractions of 250 c.c. were collected. Subfractions 1—7 were negligible. Subfraction 8 (325 mg.) gave methyl ursonate as plates (from ethanol), m. p. 191—194°, $[\alpha]_D$ +85° (*c* 1·23).

Subfraction 9 (440 mg.) crystallised from ethanol, to give "*compound A*" as platelets, m. p. 147—149°, $[\alpha]_D$ +48° (*c* 1·15) (Found: C, 72·85, 73·2; H, 9·65, 9·55. $C_{32}H_{50}O_6$ requires C, 72·4; H, 9·5. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·3. $C_{33}H_{52}O_6$ requires C, 72·75; H, 9·6%), $\nu_{max.}$ (in CS_2) 1727, 1190, and 1140 cm.$^{-1}$, $\nu_{max.}$ (in CCl_4; spectrum determined on a "Unicam" S.P. 100 infrared spectrophotometer) 1727 (ε_a 990), shoulder 1739 (ε_a 635), $\Delta\nu_{\frac{1}{2}}^{a} = 25$ cm.$^{-1}$, $B = 5{\cdot}0 \times 10^4$ mole^{-1} l. cm.$^{-2}$.

Subfraction 10 could not be recrystallised. Subfractions 11—12 (750 mg.) were recrystallised from aqueous methanol, to give methyl dammarenolate as needles, m. p. 88—92°, $[\alpha]_D$ +44° (*c* 1·32). Subfractions 14—15 gave small amounts of "compound B," m. p. 212—218°.

Hydrolysis of Methyl Asiatate (*Methyl Dammarolate*).—The ester (100 mg.) in ethylene glycol (10 c.c.) was heated under reflux for 20 hr. with potassium hydroxide (750 mg.). After acidification with hydrochloric acid and dilution with water, extraction with chloroform yielded a product which was crystallised from acetone to give asiatic acid, m. p. *ca.* 318° (decomp.), $[\alpha]_D$ (in EtOH) +48° (*c* 0·56).

	ε at stated λ			
	2220 Å	2150 Å	2100 Å	2050 Å
Methyl ursonate	1080	2540	4550	6150
Methyl asiatate	600	1730	3080	4050
"Compound A"	810	2130	4080	5800
"Compound B"	725	1960	3710	4910

Action of Lead Tetra-acetate on Methyl Asiatate (*Methyl Dammarolate*).—The ester (4·44 mg.) was treated with a standard solution (2 c.c.) of lead tetra-acetate in acetic acid at 20° for 16 hr. After this time 0·82 mol. of lead tetra-acetate had been consumed.

Hydrolysis of "Compound B."—"Compound B" (28 mg.) was kept at 20° in 10% methanolic potassium hydroxide (15 c.c.) for 48 hr. After acidification and dilution with water, ethereal extraction afforded an amorphous solid, $\nu_{max.}$ 3610, 1727, 1715 (sh), 1433, 1143, and 1109 cm.$^{-1}$.

Dehydration of Methyl Tetrahydrodammarenolate and Ozonolysis of the Products.—Methyl tetrahydrodammarenolate [3] (V) (500 mg.), m. p. 105—106°, $[\alpha]_D$ +29°, was treated in pyridine (10 c.c.) with phosphorus oxychloride and the mixture kept for 4 hr. Dilution with water and extraction with ether afforded an oil (470 mg.), $\nu_{max.}$ (liquid film) 1736, 1650, 1167, and 870 (broad) cm.$^{-1}$, giving a yellow colour with tetranitromethane. The oil in acetic acid (40 c.c.) was treated with 6% ozonised oxygen for 25 min. Zinc dust (500 mg.) and water (50 c.c.) were added and the mixture steam-distilled. The distillate (60 c.c.) was neutralised to phenolphthalein with 40% sodium hydroxide solution, and then 2,4-dinitrophenylhydrazine (300 mg.) in 2N-hydrochloric acid was added. The resulting 2,4-dinitrophenylhydrazones were extracted with benzene and the extract dried ($MgSO_4$) and filtered through alumina (activity II) (150 g.) to remove 2,4-dinitrophenylhydrazine. The filtrate was evaporated and the residue (90 mg.) was chromatographed on bentonite (24 g.)–kieselguhr (6 g.). Elution with benzene afforded isohexanal 2,4-dinitrophenylhydrazone as yellow plates (25%) (from methanol), m. p. and mixed m. p. 96—97°, and formaldehyde 2,4-dinitrophenylhydrazone as yellow needles (20%) (from methanol), m. p. and mixed m. p. 164—166°.

Preparation of a Diphenyl-alcohol (VI) *from Methyl Tetrahydrodammarenolate.*—Methyl tetrahydrodammarenolate (500 mg.) in ether (5 c.c.) was treated with ~1·7M-ethereal phenylmagnesium bromide (3 c.c.). The mixture was heated under reflux for 1·5 hr. and kept for 24 hr. After dilution with ammonium chloride solution the product was isolated with ether. Crystallisation from slightly aqueous methanol or light petroleum gave the *alcohol* (VI) as plates, m. p. 151—153°, $[\alpha]_D$ +24° (*c* 0·94) (Found: C, 83·55; H, 10·45. $C_{43}H_{64}O_2$ requires C, 83·95; H, 10·7%), $\nu_{max.}$ (in CS_2) 3497, 3003, 750, and 698 cm.$^{-1}$, $\lambda_{max.}$ 2590 Å (ε 610).

Dehydration of the Alcohol (VI).—The alcohol (200 mg.) was heated under reflux in acetic acid (5 c.c.) containing acetic anhydride (1 c.c.) for 4 hr. The solvent was removed and the resulting oil was filtered through alumina (activity I), to give an oil (150 mg.), $\nu_{max.}$ 1590, 775, 763, and 702 cm.$^{-1}$, $\lambda_{max.}$ 2525 Å (ε 17,400).

XUM

Reduction of Methyl Tetrahydrodammarenolate with Lithium Aluminium Hydride.—The methyl ester (500 mg.) in ether (100 c.c.) was heated under reflux with lithium aluminium hydride (300 mg.) for 3 hr. The excess of hydride was destroyed with ethyl acetate, and the ethereal phase was washed with 2N-sulphuric acid. Evaporation of the ethereal solution afforded a solid which crystallised from 10% aqueous methanol to give the *diol* (VII) as plates, m. p. 125—126°, $[\alpha]_D$ +32° (*c* 1·07) (Found: C, 80·45; H, 12·4. $C_{30}H_{56}O_2$ requires C, 80·3; H, 12·6%), $\nu_{max.}$ (in CS_2) 3534 and 1050 cm.$^{-1}$. Acetic anhydride–pyridine afforded a monoacetate, needles, m. p. 123—126°, $[\alpha]_D$ +33° (*c* 1·36), $\nu_{max.}$ (in CS_2) 3534, 1734, 1232, and 1030 cm.$^{-1}$.

Side-chain Determination[10] *with Methyl Tetrahydrodammarenolate.*—The methyl ester (120 mg.) together with two drops of benzenesulphonyl chloride was heated at 400° for 2 hr. The pyrolysed mixture was distilled at 200° for ½ hr. and the distillate was dissolved in ether and examined by vapour-phase chromatography. It was found to contain 2-methylheptane and 2-methylheptene as its major constituents.

Hydrolysis of Methyl Dammarenolate.—The methyl ester (250 mg.) in 10% ethanolic potassium hydroxide was kept at 20° for 48 hr. After acidification ether-extraction afforded an oil which was chromatographed on silica gel (25 g.). Elution with ether–benzene (1 : 4) gave a fraction which on crystallisation from aqueous methanol or light petroleum gave dammarenolic acid in a new polymorphic *form* as needles, m. p. 95—100°, $[\alpha]_D$ +39° (*c* 1·04) (Found: C, 78·7; H, 11·0. $C_{30}H_{50}O_2$ requires C, 78·55; H, 11·0%), $\nu_{max.}$ (in CS_2) 3500, 3030, 1704, 1016, and 890 cm.$^{-1}$. When the polymorph was dissolved in aqueous methanol, and the solution seeded with a sample of dammarenolic acid, m. p. 135—140°, $[\alpha]_D$ +42° (kindly supplied by Dr. J. S. Mills and Professor C. Djerassi), needles of m. p. 138—141° were obtained. The infrared spectra (CS_2) of the two polymorphs were identical.

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131. *The Synthesis of Some Thiophens Related to Vitamin A.*

By R. M. ACHESON, J. A. BARLTROP, M. HICHENS, and R. E. HICHENS.

Perhydro-2,2- and -4,4-dimethyl- and -2,4,4-trimethyl-3-oxothiophen have been synthesised by cyclisation of the corresponding dicarboxylic acids in the presence of barium hydroxide. The ethynylcarbinols, obtained from the last two ketones, gave with crotonylideneacetone or 6-methylocta-3,5,7-trien-2-one the expected ditertiary alcohols which rearranged with acid to the more conjugated tertiary-secondary and tertiary-primary alcohols respectively. Reduction of the products from 6-methylocta-3,5,7-trien-2-one with lithium aluminium hydride gave perhydro-3-hydroxy-3-(9-hydroxy-3,7-dimethylnona-1,3,5,7-tetraenyl)-4,4-dimethyl- and -2,4,4-trimethyl-thiophen which soon polymerised.

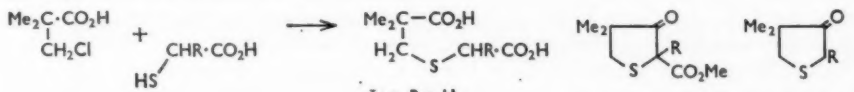
MANY analogues of vitamin A have been synthesised and the growth-promoting properties in rats of a proportion of these compounds have been measured relative to that of vitamin A itself.[1] It is unfortunate that biological data are not available for all the analogues prepared, and it is particularly regrettable that, with one exception, no tests of possible anti-vitamin A activity have been reported. The one exception is a mixture of two compounds which is claimed [2] to possess anti-vitamin A activity and was prepared [2] from vitamin A by oxidation with vanadium tetroxide; the structures of the constituents have not been convincingly demonstrated. The ingestion of certain chlorinated naphthalenes

[1] Milas, in "The Vitamins," Vol. I, ed. Sebrell and Harris, Academic Press, New York, 1954; Bharucha and Weedon, *J.*, 1953, 1571.

[2] Meunier, Jouanneteau, and Ferrando, *Compt. rend.*, 1950, **230**, 140; Meunier, *Fortschr. Chem. org. Naturstoffe*, 1952, **9**, 102; Meunier, Zwingelstein, Jouanneteau, and Mallein, *Compt. rend.*, 1950, **230**, 1323.

can cause a condition that resembles the symptons of vitamin A deficiency,[3,4] but the functions of vitamin A *in vivo*, with the exception [5] of the cycle involving the retinenes in the eye, are not understood [6] and experiments [7] involving ^{14}C-labelled vitamin A have so far thrown little light on the problem. As structural analogues have proved useful in other instances in investigating the function of compounds essential to animal life the synthesis of some potential anti-vitamin A compounds was undertaken.

Although the cyclohexene ring can be modified in vitamin A analogues without total loss of growth-promoting activity, alteration in the side chain usually leads to activity only when conversion into the vitamin *in vivo* is possible. This, coupled with the fact that the replacement of two carbon atoms by sulphur, and *vice versa*, has led to anti-metabolite activity in the cases of nicotinamide and thiazole-5-carboxyamide,[8] phenylalanine and thienylalanine,[9] biotin and ureidocyclohexylvaleric acid,[10] and thiamine and pyrithiamine,[11] suggested the synthesis of the dihydrothiophen analogues of vitamin A. Comparatively little is known about dihydrothiophens; the 2,3-isomer polymerises slowly at room temperature or on prolonged heating,[12] but the 2,5-isomer is reported to be stable.[12] It was therefore considered worth while to try to synthesise both the 2,3- and the 2,5-dihydrothiophen analogues of vitamin A, and most of the experiments described here are in connexion with the former compound (XIV).

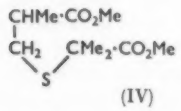


The route chosen was based on the synthesis of vitamin A carried out by Attenburrow *et al.*,[13] and the preparation of the requisite ketones was undertaken. Perhydro-4,4-dimethyl-3-oxothiophen (IIIa) was prepared by cyclisation of dimethyl ester of the acid (Ia); the corresponding sequence involving the diethyl ester had been described previously.[14] A number of attempts to methylate the intermediate keto-ester (IIa) at position 2, with a view to obtaining the trimethylthiophen derivatives (IIb) and (IIIb), were unsuccessful as ionic products were invariably formed. 3-Chloropivalic acid was then condensed with α-mercaptopropionic acid, and a number of attempts were made to cyclise the methyl ester of the product (Ib). As only one α-hydrogen atom is present triphenylmethylsodium was used as the condensing agent, and in most experiments perhydro-2,4,4-trimethyl-3-oxothiophen (IIIb) was obtained in poor yield. On one occasion, unaccountably, a liquid with a higher boiling point than the oxothiophen (IIIb) was obtained. Its composition was that required of the keto-ester (IIb), but hydrolysis under conditions successful for the corresponding dimethyl compound (IIa) gave none of the desired ketone (IIIb). Attempts to cyclise the isomeric ester (IV) [which had been

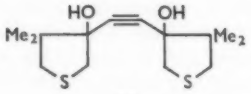
[3] Engel and Bell, *Nutrit. Abs. Rev.*, 1953, **11**, 97.
[4] Editorial, *Nutrit. Abs. Rev.*, 1954, **12**, 180; Ferrando, *ibid.*, 1957, **15**, 319; Hove, *J. Nutrit.*, 1953, **51**, 609.
[5] Morton and Pitt, *Fortschr. Chem. org. Naturstoffe*, 1957, **14**, 244; Dartnell, "The Visual Pigments," Methuen, London, 1957.
[6] Lowe and Morton, *Vitamins and Hormones*, 1956, **14**, 97.
[7] Wolf, Lane, and Johnson, *J. Biol. Chem.*, 1957, **225**, 995; Wolf, Kahn, and Johnson, *J. Amer. Chem. Soc.*, 1957, **79**, 1208.
[8] Erlenmeyer and Wurgler, *Helv. Chim. Acta*, 1942, **25**, 249; Erlenmeyer, Bloch, and Kiefer, *ibid.*, 1942, **25**, 1066.
[9] Garst, Campaigne, and Day, *J. Biol. Chem.*, 1949, **180**, 1013.
[10] English, Clapp, Cole, Halverstadt, Lampen, and Roblin, *J. Amer. Chem. Soc.*, 1945, **67**, 295.
[11] Woolley and White, *J. Biol. Chem.*, 1943, **149**, 285.
[12] Birch and McAllan, *J.*, 1951, 2556.
[13] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[14] Truce and Knospe, *J. Amer. Chem. Soc.*, 1955, **77**, 5063.

XUM

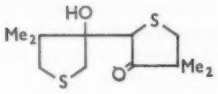
prepared by base-catalysed (Michael) addition of methyl α-mercapto-α-methylpropionate to methyl methacrylate] with triphenylmethylsodium were less successful. No cyclisation could be detected and a reverse Michael reaction, as sometimes occurs in the presence of molar quantities of strong bases, took place. At this stage it was found that the pyrolysis of the acid (Ia) over barium hydroxide gave the ketone (IIIa) in excellent yield, and the reaction has been applied with success to the synthesis of the trimethyl analogue (IIIb) and of perhydro-2,2-dimethyl-3-oxothiophen.



(IV)



(V)

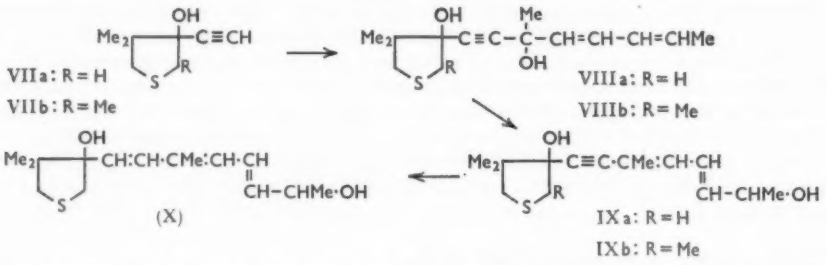


(VI)

In contrast to 2,2,6-trimethylcyclohexanone, perhydro-2,4,4-trimethyl-3-oxothiophen does not react with 2,4-dinitrophenylhydrazine, although it yields a semicarbazone. The failure may be due to steric hindrance as the corresponding dimethyl compound (IIIa) yields a 2,4-dinitrophenylhydrazone without difficulty. Oxidation of the trimethyl-ketone (IIIb) with hydrogen peroxide did not give the expected sulphone: the ring was opened giving di-(2-carboxy-2-methylpropyl) disulphide, which had been obtained earlier by a similar oxidation of perhydro-4,4-dimethyl-3-oxothiophen.[14]

Ethynylation of the ketones (IIIa, b) has been tried under a variety of conditions with only moderate success. 3-Ethynylperhydro-3-hydroxy-4,4-dimethylthiophen (VIIa) was obtained with least difficulty from the ketone (IIIa), acetylene, and calcium acetylide in liquid ammonia; a small amount of the glycol (V) was also isolated. When the ethynylation was effected with ethynylmagnesium bromide in tetrahydrofuran [15] it proved much more difficult to isolate the desired product and a small amount of the aldol (VI) was formed. In the case of the trimethyl-ketone (IIIb), however, the corresponding ethynyl-carbinol (VIIb) was best prepared by the ethynylmagnesium bromide method.

Both ethynylcarbinols (VII) gave bismagnesium derivatives with ethylmagnesium bromide, and these combined with hepta-3,5-dien-2-one which had been prepared and



purified by the method of Attenburrow *et al.*[13] The products were the ditertiary alcohols (VIII) which isomerised in the presence of acid to the more highly conjugated secondary-tertiary alcohols (IX). The ditertiary alcohols (VIII) showed infrared absorption at 1709 cm.$^{-1}$, and their isomers (IX) at 1710 cm.$^{-1}$. Such absorption in the carbonyl region has been observed previously [16] for acetylenic compounds carrying functional groups on a carbon atom directly attached to the acetylene group although the origin of the absorption is not clear.

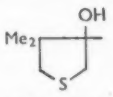
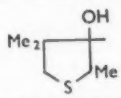
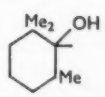
Reduction of the acetylenic bond in (IXa) was achieved with lithium aluminium

[15] Jones, Skattebol, and Whiting, 1956, 4765.
[16] Wotiz, Miller, and Palchak, *J. Amer. Chem. Soc.*, 1950, **72**, 5055; Wotiz and Miller, *ibid.*, 1949, **71**, 3441.

hydride, and oxidation of the product (X) with manganese dioxide gave a poor yield of perhydro-3-hydroxy-4,4-dimethyl-3-(6-methyl-2-oxo-octa-3,5,7-trienyl)thiophen. Much material remained adsorbed on the manganese dioxide, as was the case in the similar oxidation of the secondary alcohol (IXb) to the corresponding ketone. The ultraviolet absorption spectra of all these products based on the heptadienone are very similar to those of the corresponding derivatives in the 2,2,6-trimethylcyclohexanol series (Table) and thus confirm their structures.

As the experiments with hepta-3,5-dien-2-one were successful, 6-methylocta-3,5,7-trien-2-one was prepared by the modifications introduced by Attenburrow *et al.*[13] into the five-stage synthesis used by Cheeseman *et al.*[17] This ketone condensed with the bismagnesium

Ultraviolet absorption data [$\lambda_{max.}$ (Å); $10^{-4}\varepsilon$ *in parentheses*] *for the perhydrothiophens and their cyclohexane analogues.*

Compound	Formula	Cyclic substituent R					
							
R·C≡C·CMe(OH)·CH=CH·CH=CHMe	(VIII)	2290	(2·86)	2285	(2·80)	2290	(2·50)
R·C≡C·CMe=CH·CH=CH·CHMe·OH	(IX)	2685	(2·98)	2680	(3·25)	2690	(3·23)
		2795	(2·31)	2790	(2·30)	8200	(2·36)
R·C≡C·CMe=CH·CH=CH·COMe semicarbazone	—	—	—	2290*	(0·54)	2320*	(0·43)
		—	—	3180	(3·60)	3160	(4·98)
		—	—	3325	(3·17)	3330	(4·35)
R·CH=CH·CMe=CH·CH=CH·CHMe·OH	(X)	2655	(3·00)	—	—	2650	(2·34)
		2755	(3·58)	—	—	2740	(2·82)
		2850	(2·66)	—	—	2850	(2·24)
R·CH=CH·CMe=CH·CH=CH·COMe semicarbazone	—	2340	(0·25)	—	—	2350	(0·49)
		3100	(4·23)	—	—	—	—
		3220	(5·60)	—	—	3250	(5·75)
		3370	(4·68)	—	—	3400	(4·86)
R·C≡C·CMe(OH)·CH=CH·CH=CMe·CH=CH_2	(XI)	2590–2630*	(3·25)	2590–2630*	(3·14)	—	—
		2690	(4·10)	2690	(3·98)	2700	(4·06)
		2800	(3·25)	2800	(3·14)	2810	(3·16)
R·C≡C·CMe=CH·CH=CH·CMe=CH·CH_2·OH	(XII)	2250	(1·04)	2260	(0·92)	2260	(0·84)
		2880–2935*	(4·70)	2880–2935*	(3·57)	2870–2960*	(3·57)
		3010	(6·39)	3010	(4·95)	3020	(4·76)
		3150	(5·29)	3150	(4·08)	3170	(3·94)
Anthraquinone-2-carboxylate of (XII)		2590	(6·19)	2580	(5·15)	2580	(6·25)
		2780	(4·07)	2760	(3·30)	2800	(3·14)
		2940–2965*	(4·55)	2930–2960*	(3·82)	—	—
		3060	(5·81)	3050	(4·80)	3060	(4·16)
		3210	(4·94)	3190	(4·14)	3200	(3·80)
R·CH=CH·CMe=CH·CH=CH·CMe=CH·CH_2·OH	(XIII)	2290	(0·68)	2260	(0·74)	2300	(0·57)
		2835–2860*	(2·44)	2835–2855*	(2 86)	—	—
		2950	(4·04)	2950	(4·40)	2960	(4·35)
		3075	(5·29)	3070	(5·93)	3070	(5·80)
		3220	(4·18)	3225	(4·65)	3230	(4·66)

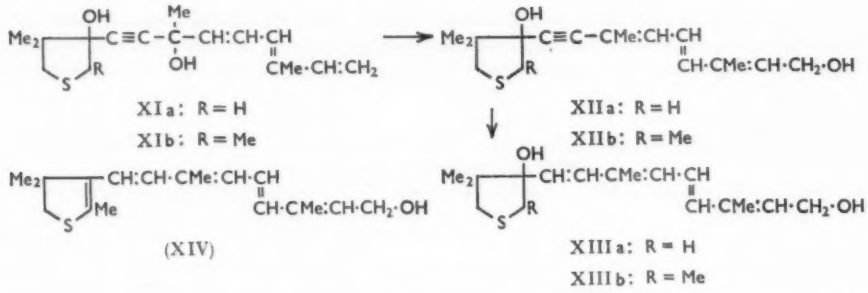
* Inflexion.

derivatives of the ethynylcarbinols (VII), and the products (XI) rearranged with acid to the more highly conjugated primary alcohols (XII). Three crystalline modifications of one of these (XIIb) were obtained and, although all had identical ultraviolet absorption spectra, the identical infrared absorption spectra (determined in paraffin paste) of the two lower-melting modifications differed in small ways from that of the highest-melting

[17] Cheesman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031.

XUM

modification. Reduction of the diols (XII) by lithium aluminium hydride gave only a 5% yield of the alcohol (XIIIa) and 20% of the analogue (XIIIb) in contrast to the good yields obtained in the corresponding stage of the vitamin A synthesis; and the ether-soluble material left after the reduction was only about half the weight of the starting material. There is little in the literature to suggest that the hydride would cause sulphur–carbon scission, and it is likely that polymerisation of the reduced diols took place. Both



diols were unstable and in the case of (XIIIa) the best crystalline sample obtained deteriorated rapidly at 0° under nitrogen. No satisfactory analysis was obtained for this compound although the light absorption indicates that the material was substantially pure when these measurements were made. The trimethylthiophen derivative (XIIIb) was obtained analytically pure and was characterised as the acetate, but sufficient material was not obtained to attempt dehydration to the vitamin A analogue (XIV). The ultraviolet absorption spectra of the perhydrothiophens (Table) were very similar to those of the corresponding cyclohexanes.[13]

Experimental

The alumina used for chromatography was Spence type H, 100—200 mesh, which had been deactivated by shaking it with 5% of its weight of 10% aqueous acetic acid. The light petroleum used had b. p. 40—60°. Magnesium sulphate was used as the drying agent, unless otherwise specified. The solvent ratios in mixed solvents are all v/v. Polyenes were distilled under nitrogen, and fractionations were through a 24″ vacuum-jacketed, heated column filled with Dixon rings or glass helices. The ultraviolet absorption spectra were measured for EtOH solutions. Alkali-washings of ether extracts were with sodium hydrogen carbonate solution.

(*Carboxymethylthio*)*pivalic acid*.—Mercaptoacetic acid (200 g.) in aqueous potassium hydroxide (286 g. in 500 ml.) was added to chloropivalic acid [18] (324 g.) in aqueous sodium carbonate (130 g. in 1 l.), and after 6 hours' refluxing the mixture was acidified and extracted with ether. Distillation of the dried extract gave (*carboxymethylthio*)*pivalic acid* (280 g.) as a yellow viscous oil, b. p. 154°/0·02 mm. (Found: C, 43·7; H, 6·7; S, 16·6. $C_7H_{12}O_4S$ requires C, 43·7; H, 6·3; S, 16·2%). This solidified to a glass which resisted all attempts at crystallisation.

This acid (25 g.) was heated under reflux with methanol (120 ml.) containing hydrogen chloride (6 g.) for 5 hr. and then the excess of methanol was removed *in vacuo*. The residue, in ether, was washed with aqueous sodium hydrogen carbonate, dried, and distilled, and gave the *ester* (18 g.), b. p. 104—106°/0·05 mm., n_D^{10} 1·4734 (Found: C, 49·3; H, 7·3; S, 14·5. $C_9H_{16}O_4S$ requires C, 49·1; H, 7·3; S, 14·5%).

Methyl Perhydro-4,4-dimethyl-3-oxothiophen-2-carboxylate (IIa).—The preceding ester (9·0 g.) in dry toluene (75 ml.) was stirred at 50° for 5 hr. with sodium methoxide (1·4 g.), and the mixture left at room temperature for 2 days. Acetic acid (10 ml.), ice, and ether were added. An ether extract was made and washed with aqueous sodium hydrogen carbonate, dried, and distilled, giving the *keto-ester* (5·0 g.), b. p. 78—79°/1 mm., n_D^{10} 1·4950 (Found: C, 50·6; H, 6·4; S, 16·9. $C_8H_{12}O_3S$ requires C, 51·0; H, 6·4; S, 17·0%). The *2,4-dinitrophenylhydrazone*

[18] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 925.

separated from methanol in orange needles, m. p. 122° (Found: C, 45·5; H, 4·3. $C_{14}H_{16}N_4O_6S$ requires C, 45·6; H, 4·5%).

Perhydro-4,4-dimethyl-3-oxothiophen (IIIa).—(i) The preceding ester (5·0 g.) was heated under reflux with 2N-sulphuric acid (40 ml.) for 4 hr. and extracted with ether. Distillation of the extract (washed with sodium hydrogen carbonate solution and dried) gave perhydro-4,4-dimethyl-3-oxothiophen (2·0 g.), b. p. 62—63°/10 mm., n_D^{19} 1·4970 (Found: C, 55·0; H, 7·7; S, 24·8. Calc. for $C_6H_{10}OS$: C, 55·3; H, 7·7; S, 24·6%). Truce and Knospe [14] give b. p. 78—78·5°/20 mm. and n_D^{25} 1·4948 but do not describe derivatives. The *2,4-dinitrophenylhydrazone*, orange needles from methanol, had m. p. 125° (Found: C, 45·9; H, 4·7. $C_{12}H_{14}N_4O_4S$ requires C, 46·3; H, 4·5%), and the *semicarbazone*, colourless needles from water, had m. p. 205° (Found: C, 44·9; H, 7·0; N, 22·1. $C_7H_{13}N_3OS$ requires C, 44·9; H, 7·0; N, 22·4%).

(ii) (Carboxymethylthio)pivalic acid (270 g.) was heated to 200° with finely powdered barium hydroxide (10 g.). The non-aqueous layer of the distillate was dried ($CaCl_2$), and distillation gave perhydro-4,4-dimethyl-3-oxothiophen (140 g.), b. p. 60—62°/6 mm., with refractive index, infrared absorption spectrum, and semicarbazone identical with those of the compound prepared as under (i).

α-Mercaptopropionic Acid.—α-Chloropropionic acid (21 g.) and thiourea (15 g.) were refluxed in ethanol (50 ml.) for 1 hr. *2-Amino-4-hydroxy-5-methylthiazole hydrochloride* separated on cooling, and after crystallisation from ethanol had m. p. 200° (26 g.) (Found: C, 28·8; H, 4·3; N, 16·6; S, 18·9. $C_4H_6N_2OS,HCl$ requires C, 28·8; H, 4·2; N, 16·8; S, 19·2%). This hydrochloride was heated under reflux with 10% aqueous sodium hydroxide (250 ml.) for 3 hr., acidified, and extracted with ether. Distillation of the dried extract gave α-mercaptopropionic (thiolactic) acid, b. p. 97—98°/8 mm., n_D^{13} 1·4827, as a foul-smelling colourless liquid (7 g.). Dixon [19] has described the preparation of the thiazole hydrochloride in outline, but gave no analysis, and he mentioned its decomposition with barium hydroxide to thiolactic acid.

(1-Carboxyethylthio)pivalic Acid.—α-Mercaptopropionic acid (240 g.) and potassium hydroxide (350 g.) in water (1 l.) were added to chloropivalic acid (300 g.) and sodium hydrogen carbonate (200 g.) in water (800 ml.), and the mixture was refluxed for 18 hr. After acidification, with ice-cooling, the mixture was extracted with ether, and the extract washed with water and dried. Distillation gave a viscous oil, b. p. 172°/0·03 mm. (324 g.), which solidified. Recrystallisation from light petroleum gave the *acid* as colourless rhombs, m. p. 83° (Found: C, 46·9; H, 6·8; S, 15·7. $C_8H_{14}O_4S$ requires C, 46·6; H, 6·8; S, 15·6%).

This acid (2·3 g.) and 30% hydrogen peroxide (4 ml.) were mixed in glacial acetic acid, heat being evolved. After being kept overnight the mixture was heated under reflux for 3 hr. and evaporated to dryness *in vacuo*. The residue on crystallisation from ethyl acetate–light petroleum gave the *sulphone* (1·5 g.) as colourless needles, m. p. 149·5—150·5° (Found: C, 40·5; H, 6·1; S, 12·9. $C_8H_{14}O_6S$ requires C, 40·3; H, 5·9; S, 13·4%).

Methyl (1-methoxycarbonylethylthio)pivalate, obtained from the crude acid and hydrogen chloride in methanol in the usual way, in 73% yield, had b. p. 86—88°/0·06 mm., n_D^{12} 1·4699 (Found: C, 51·5; H, 7·9; S, 13·4. $C_{10}H_{18}O_4S$ requires C, 51·3; H, 7·7; S, 13·7%).

Perhydro-2,4,4-trimethyl-3-oxothiophen (IIIb).—(i) The preceding ester (7·4 g.) was added under nitrogen to triphenylmethylsodium, prepared from triphenylmethyl chloride (11 g.) and 1% sodium amalgam (200 g.), in ether (270 ml.). The intense red colour was discharged immediately and, after 24 hr., acetic acid (2 g.) was added. The mixture was washed with aqueous sodium hydrogen carbonate, dried, and evaporated and ethanol containing 5% of water was added. Triphenylmethane was precipitated and was collected, and distillation of the filtrate gave first ethanol, which smelled strongly of mercaptan and gave a red colour with sodium nitroprusside (it was not investigated further), and then *perhydro-2,4,4-trimethyl-3-oxothiophen* (1·0 g.), b. p. 78°/16 mm., n_D^{19} 1·4963 (Found: C, 58·0; H, 8·0; S, 22·7. $C_7H_{12}OS$ requires C, 58·4; H, 8·3; S, 22·2%). The *semicarbazone* separated from aqueous ethanol in needles, m. p. 188° (Found: C, 48·0; H, 7·5; S, 15·8. $C_8H_{15}N_3OS$ requires C, 47·8; H, 7·5; S, 15·9%). Higher-boiling fractions were the initial diester, b. p. 82°/0·2 mm. (2·5 g.), and triphenylmethane, b. p. 134°/0·2 mm.

On one occasion, instead of the expected product, the above experiment yielded a pale yellow oil, b. p. 85—90°/0·5 mm., n_D^{16} 1·4780, which appeared to be *methyl perhydro-2,4,4-trimethyl-3-oxothiophen-2-carboxylate* (IIb) (15% yield) (Found: C, 53·0; H, 6·7; S, 16·0. $C_9H_{14}O_3S$ requires C, 53·4; H, 6·9; S, 15·8%). Attempted hydrolysis of this oil (1·9 g.) by

[19] Dixon, *J.*, 1893, 819.

heating it under reflux for 5 hr. with 2N-sulphuric acid (20 ml.) followed by ether-extraction and distillation of the alkali-washed and dried extract gave an oily *substance* (1·5 g.), b. p. 150°/0·5 mm., that was not identified (Found: C, 58·8; H, 7·5; S, 11·5. $C_{14}H_{22}O_4S$ requires C, 58·9; H, 7·6; S, 11·3%).

(ii) (1-Carboxyethylthio)pivalic acid (270 g.) was heated to 220° with finely powdered barium hydroxide (10 g.), and the distillate (208 g.) collected. The non-aqueous layer was separated and on distillation gave perhydro-2,4,4-trimethyl-3-oxothiophen (140 g.), b. p. 60—62°/6 mm., n_D^{19} 1·4963. The semicarbazone had m. p. and mixed m. p. 188°.

Perhydro-2,4,4-trimethyl-3-oxothiophen (3·0 g.) in acetic acid (20 ml.) was mixed with 30% hydrogen peroxide (7 ml.) and after 24 hr. the solvent was removed *in vacuo*. The residual red oil partially crystallised, and recrystallisation from aqueous ethanol gave di-(2-carboxy-2-methylpropyl) disulphide as colourless plates, m. p. 145—146° (Found: C, 44·6; H, 6·6; S, 24·1. Calc. for $C_{10}H_{18}O_4S_2$: C, 45·1; H, 6·8; S, 24·0%) (lit.,[14] m. p. 147·5—148·5°).

α-(2-*Carboxyethylthio*)-α-*methylpropionic Acid*.—α-Bromo-α-methylpropionic acid (13 g.) from bromine, isobutyric acid, and its anhydride in the presence of pyridine, was neutralised with sodium hydroxide and added to β-mercaptopropionic acid (8·5 g.) in 5% aqueous sodium hydroxide (120 ml.). After 12 hr. the mixture was heated under reflux for 5 hr., cooled, acidified with hydrochloric acid, and extracted with ether. Distillation of the dried extract gave the substituted *propionic acid* (3·2 g.), b. p. 170—180°/0·03 mm., which solidified. It separated from light petroleum as colourless crystals, m. p. 53° (Found: C, 43·5; H, 6·3; S, 16·4. $C_7H_{12}O_4S$ requires C, 43·7; H, 6·2; S, 16·7%).

Perhydro-2,2-dimethyl-3-oxothiophen.—The preceding acid (2·5 g.) was heated at 200—220° with finely powdered barium hydroxide (0·1 g.), and the distillate collected with ether and dried ($MgSO_4$). Distillation gave the *ketone* (1·0 g.), b. p. 115—120°/18 mm., n_D^{17} 1·4532 (Found: C, 55·5; H, 7·8; S, 24·3. $C_6H_{10}OS$ requires C, 55·3; H, 7·7; S, 24·6%).

Methyl α-Mercapto-α-methylpropionate.—Sodium hydrogen sulphide in methanol, prepared by passing hydrogen sulphide into a solution of sodium (9·2 g.) in dry methanol (80 g.) until the required increase in weight (13 g.) had taken place, was added to methyl α-bromo-α-methylpropionate (30 g.), and the mixture refluxed for 40 min. Precipitated sodium bromide was removed and the filtrate was acidified with acetic acid, diluted to 500 ml. with water, and extracted with benzene. The extract was alkali-washed, dried, and distilled, giving the ester (8 g.) as an evil-smelling liquid, b. p. 86°/100 mm.

Methyl α-(2-*Methoxycarbonylpropylthio*)-α-*methylpropionate* (IV).—Freshly redistilled methyl methacrylate (11 g.) was added dropwise to methyl α-mercapto-α-methylpropionate (8 g.) containing sodium methoxide (0·1 g.) with stirring during 30 min., and stirring continued for a further 90 min. After filtration the mixture was distilled and gave the *diester* (10 g.), b. p. 64—66°/0·02 mm., n_D^{17} 1·4683 (Found: C, 51·5; H, 7·8; S, 13·4. $C_{10}H_{18}O_4S$ requires C, 51·3; H, 7·7; S, 13·7%).

In an attempt at cyclisation this ester (8·0 g.) was added under nitrogen to triphenylmethylsodium [from triphenylmethyl chloride (14 g.) and 1% sodium amalgam (300 g.)] in ether (300 ml.), and the mixture shaken for 6 hr. The precipitate was collected, suspended in ether, and acidified with acetic acid (2 ml.). Evaporation and distillation yielded only methyl α-mercapto-α-methylpropionate (2·0 g.), b. p. 87°/100 mm., which was characterised as its *S*-triphenylmethyl derivative, m. p. 148—150° (Found: C, 75·9; H, 6·1. Calc. for $C_{23}H_{22}O_2S$: C, 76·2; H, 6·1%) (lit.,[20] gives m. p. 155—156°).

3-*Ethynylperhydro-4,4-dimethylthiophen-3-ol* (VIIa).—(i) Liquid ammonia (3 l.) was saturated with dry, acetone-free acetylene, and calcium turnings (30 g.) were added during 2 hr. with stirring. The stream of acetylene was continued while perhydro-4,4-dimethyl-3-oxothiophen (70 g.) in ether (70 ml.) was added dropwise, and after overnight stirring ammonium chloride (100 g.) was added cautiously. The ammonia was allowed to evaporate, the residue was extracted with ether, and the extracts were washed with water and dried. Distillation gave first pure perhydro-4,4-dimethyl-3-oxothiophen (20 g.), and then a mixture of this and the desired product which had b. p. 92—108°/17 mm., n_D^{23} 1·5030, and could not be resolved by further fractionation. The next fraction was a colourless oil (18 g.), b. p. 117—124°/17 mm., n_D^{23} 1·5160—1·5250, that solidified slowly and crystallised from light petroleum giving the *ethynylcarbinol*, m. p. 38° (Found: C, 61·3; H, 7·9; S, 20·6. $C_8H_{12}OS$ requires C, 61·5; H, 7·8; S, 20·5%). The presence of the ethynyl group was shown by absorption at 2210 cm.$^{-1}$.

[20] Iskander and Tewkif, *J.*, 1951, 2050.

XUM

The residue from the distillation solidified overnight, and crystallisation from benzene gave a colourless solid, m. p. 132°, which showed absorption in the hydroxyl region (3400 cm.$^{-1}$) and may be *bis(perhydro-3-hydroxy-4,4-dimethyl-3-thienyl)acetylene* (V) (Found: C, 58·9; H, 7·5; S, 22·6. $C_{14}H_{22}O_2S_2$ requires C, 58·7; H, 7·7; S, 22·4%).

Poorer results were obtained when the initial reaction mixture was allowed to remain at room temperature in a steel bomb for 2 days before being worked up.

(ii) Perhydro-4,4-dimethyl-3-oxothiophen (18·2 g.) in an equal volume of dry tetrahydrofuran was added to ethynylmagnesium bromide (from 4·8 g. of magnesium) in tetrahydrofuran (220 ml.), prepared according to Jones *et al.*,[15] with ice-cooling. After overnight stirring saturated aqueous ammonium chloride was added. The organic layer, combined with ether extracts of the aqueous layer, was washed with water, dried, and evaporated, and the residual oil (20 g.) treated with a small quantity of light petroleum. A colourless solid (1·7 g.) separated at 0°, and after crystallisation from benzene had m. p. 79°. Absorption at 3510 and 1735 cm.$^{-1}$ indicated the presence of hydroxyl and carbonyl groups respectively, and the compound is tentatively formulated as *perhydro-4,4-dimethyl-3-oxo-2-(perhydro-3-hydroxy-4,4-dimethyl-3-thienyl)thiophen* (VI) (Found: C, 55·2; H, 7·9; S, 24·3. $C_{12}H_{20}O_2S_2$ requires C, 55·4; H, 7·7; S, 24·6%).

The remainder of the product (18·3 g.) was chromatographed on alumina. Elution with light petroleum and with benzene gave oils, which were combined, and subsequent elution with ether gave some of the bisthienylacetylene described under (i), as shown by m. p. and infrared absorption spectrum comparisons. The oils (9·7 g.) were dissolved in ethanol (100 ml.) and added dropwise to silver nitrate (48 g.) in 95% ethanol (1 l.). The colourless precipitate was collected, washed with ethanol, added to ammonium thiocyanate (30 g.) in water (108 ml.), and extracted successively with light petroleum, benzene, and ether. Evaporation of the petroleum gave a colourless oil (3·5 g.) which was not examined as the benzene fraction gave the desired ethynylcarbinol (1·3 g.); the ether extract gave a colourless solid, m. p. 140°, which was not identified. Trial experiments with the pure ethynylcarbinol showed that an 80% recovery was obtainable through the thiocyanate procedure after conversion into the silver salt.

Distillation of the crude product of an identical experiment gave an oil, b. p. 102—110°/15 mm., n_D^{12} 1·5055, which showed maxima at both 1725 and 2210 cm.$^{-1}$ and could not be resolved by further fractionation. It was treated with semicarbazide hydrochloride (6 g.) and potassium acetate (7 g.) in aqueous methanol; after warming to 60° and cooling, perhydro-4,4-dimethyl-3-oxothiophen semicarbazone was collected. The filtrate was poured into water (250 ml.) and extraction with light petroleum gave some of the ethynylcarbinol (3·7 g.), m. p. 38°.

3-Ethynylperhydro-2,4,4-trimethylthiophen-3-ol (VIIIb).—(i) Lithium (21 g.) was added in portions with stirring to liquid ammonia (4 l.) previously saturated with acetylene, while the acetylene stream was continued. Perhydro-2,4,4-trimethyl-3-oxothiophen (180 g.) in ether (500 ml.) was added in 1 hr. and stirring continued for 2 hr. After evaporation of the ammonia, ammonium chloride and ice were added, and the mixture was extracted with ether. Distillation of the washed, dried extracts gave the original ketone (89 g.) and a brown oil, b. p. 98—102°/6 mm., n_D^{21} 1·5101. Fractionation of this gave a brown liquid, b. p. 100—102°/6 mm., n_D^{19} 1·5129, containing the desired acetylene and original ketone, as shown by absorption at 2210 and 1730 cm.$^{-1}$; this mixture could not be resolved by fractionation. The liquid, in light petroleum, was chromatographed on deactivated alumina. Elution with benzene–light petroleum (1 : 1) gave *3-ethynylperhydro-2,4,4-trimethylthiophen-3-ol* (8·0 g.), m. p. 78° (from light petroleum) (Found: C, 64·0; H, 8·2. $C_9H_{14}OS$ requires C, 63·6; H, 8·2).

(ii) Perhydro-2,4,4-trimethyl-3-oxothiophen (130 g.) was added to ethynylmagnesium bromide under the same conditions as in the reaction with perhydro-4,4-dimethyl-3-oxothiophen; distillation of the crude product gave the original ketone (40 g.) and the desired ethynylcarbinol (49 g.), b. p. 108—110°/14 mm., n_D^{20} 1·5221, m. p. and mixed m. p. 78°.

The crude product from a similar reaction involving 10 g. of the perhydro-3-oxothiophen was chromatographed as above and yielded unchanged ketone (2 g.), and the ethynylcarbinol (3 g.). Final elution of the alumina with methanol gave an unidentified *substance* which separated from benzene as rhombs, m. p. 134° (Found: C, 58·6; H, 7·9; S, 19·3. $C_{16}H_{26}O_3S_2$ requires C, 58·1; H, 7·9; S, 19·4%).

Perhydro-3-hydroxy-3-(3-hydroxy-3-methylocta-4,6-dien-1-ynyl)-4,4-dimethylthiophen (VIIIa).—3-Ethynylperhydro-4,4-dimethylthiophen-3-ol (5·5 g.) in ether (10 ml.) was added dropwise to a stirred refluxing solution of ethylmagnesium bromide (from 2·1 g. of magnesium)

XUM

in ether (200 ml.), and the mixture stirred for 2 hr. Dry tetrahydrofuran was added to dissolve the precipitated complex and thus facilitate stirring. Hepta-3,5-dien-2-one [16] (5·8 g.) in tetrahydrofuran (10 ml.) was added to the mixture at 20° and the whole was stirred overnight. 20% Aqueous ammonium chloride (140 ml.) and ice were added and the product was collected with ether. The ether solution was then washed, dried, and evaporated. The residual oil, in light petroleum, was chromatographed on alumina, and elution with the same solvent, followed by benzene, gave starting materials. Elution with benzene–ether (1 : 1) gave the desired *diol* (5·36 g.) as a viscous yellow-green oil, b. p. 50°/10^{-6} mm., n_D^{13} 1·5410 (Found: C, 67·2; H, 8·1; S, 12·2. $C_{15}H_{22}O_2S$ requires C, 67·6; H, 8·3; S, 12·0%).

Perhydro-3-hydroxy-3-(7-hydroxy-3-methylocta-3,5-dien-1-ynyl)-4,4-dimethylthiophen (IXa).—The previous diol (4·0 g.) was dissolved in acetone (100 ml.), and 1% aqueous hydrochloric acid (40 ml.) was added. After 4 hr. the mixture was neutralised with saturated aqueous sodium hydrogen carbonate (150 ml.), and the product extracted with light petroleum. After drying, the extract was chromatographed on alumina. Elution with benzene–ether (1 : 1) gave the substituted *octa-3,5-dien-1-yn-7-ol* (2·8 g.) as a green-yellow viscous oil, b. p. 60°/10^{-5} mm., n_D^{12} 1·5798 (Found: C, 67·2; H, 8·1; S, 12·5. $C_{15}H_{22}O_2S$ requires C, 67·6; H, 8·3; S, 12·0%).

Perhydro-3-hydroxy-3-(7-hydroxy-3-methylocta-1,3,5-trienyl)-4,4-dimethylthiophen (X).—The octa-3,5-dien-1-yn-7-ol (IXa) (2·4 g.) in ether (50 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (0·45 g.) in ether (20 ml.), and the mixture was refluxed for 3 hr. After cooling to 0°, ice and saturated aqueous tartaric acid were added, and the ether layer was washed, dried, and evaporated; a pale yellow oil (2·1 g.), n_D^{20} 1·5650, was obtained. It was chromatographed on alumina from benzene–light petroleum (1 : 1), and elution with benzene–ether (1 : 1) gave the *octa-1,3,5-trien-7-ol derivative* (1·6 g.) as a viscous yellow oil, b. p. 60°/10^{-5} mm., n_D^{12} 1·5860 (Found: C, 66·8; H, 8·6; S, 11·5. $C_{15}H_{24}O_2S$ requires C, 67·1; H, 8·9; S, 11·9%).

Perhydro-3-hydroxy-3-(3-methylocta-1,3,5-trien-7-onyl)-4,4-dimethylthiophen.—The preceding alcohol (X) (1·4 g.) in ether (40 ml.) was shaken for 4 hr. with active manganese dioxide (15 g.), and the mixture centrifuged. Evaporation of the supernatant liquid gave a green viscous oil (0·5 g.) which was chromatographed, in benzene–light petroleum (1 : 1), on alumina. Elution with benzene–ether (1 : 1) gave the ketone as a viscous yellow oil (0·45 g.), n_D^{12} 1·6032. The *semicarbazone* crystallised from ethanol in yellow needles, m. p. 167—169° (Found: C, 59·5; H, 7·6; N, 12·7; S, 10·0. $C_{16}H_{25}N_3O_2S$ requires C, 59·5; H, 7·7; N, 13·0; S, 9·9%).

Perhydro-3-hydroxy-3-(3-hydroxy-3,7-dimethylnona-4,6,8-trien-1-ynyl)-4,4-dimethylthiophen (XIa) —3-Ethynylperhydro-4,4-dimethylthiophen-3-ol (35 g.) in benzene (300 ml.) was added slowly to ethylmagnesium bromide (from 13·2 g. of magnesium) in ether (200 ml.) and stirred under reflux for 30 min. After cooling to room temperature, 6-methylocta-3,5,7-trien-2-one [16] (31 g.) in benzene (300 ml.) was added slowly, with stirring. After refluxing for 30 min. the mixture was cooled and poured on to aqueous ammonium chloride and ice, and the organic layer was collected, washed, and dried. Evaporation gave the crude 4,6,8-trien-1-yn-3-ol derivative as a viscous brown oil (65 g.). A portion was purified by chromatography on alumina, and gave the *diol* as a viscous yellow oil, b. p. 70°/10^{-5} mm., n_D^{12} 1·5560 (Found: C, 69·7; H, 8·0; S, 11·1. $C_{17}H_{24}O_2S$ requires C, 69·9; H, 8·2; S, 10·9%).

Perhydro-3-hydroxy-3-(9-hydroxy-3,7-dimethylnona-3,5,7-trien-1-ynyl)-4,4-dimethylthiophen (XIIa).—The above crude diol (60 g.) was dissolved in 1 : 9 aqueous acetone (1 l.) containing 0·1% of sulphuric acid and left for 3 hr. at 20°, then poured into water (1·5 l.). The product was isolated with ether, and the alkali-washed extracts were dried and evaporated. The residual brown oil (59 g.; n_D^{18} 1·5550) in benzene was chromatographed on alumina. Elution with benzene–ether (1 : 1) gave a dark red oil (12 g.), n_D^{18} 1·5830, which solidified, and crystallisation from benzene gave the *3,5,7-trien-1-yn-9-ol* as yellow needles, m. p. 138—139° (Found: C, 69·6; H, 8·1; S, 11·2. $C_{17}H_{24}O_2S$ requires C, 69·9; H, 8·2; S, 10·9%).

This diol (0·2 g.) was converted into the *anthraquinone-2-carboxylate* by refluxing it with the appropriate acid chloride (0·5 g.) and pyridine (1 ml.) in dry benzene (25 ml.) for 45 min. After addition of a little water the mixture was filtered, and the benzene layer washed with dilute acid and then alkali, and water, and dried. Trituration, with ether, of the residue obtained on evaporation gave the orange ester which crystallised from benzene. It had m. p. 172°; it resolidified sharply at 178°, and decomposed on further heating without melting (Found: C, 73·1; H, 6·0; S, 6·0. $C_{32}H_{30}O_5S$ requires C, 73·0; H, 5·7; S, 6·1%).

XUM

Perhydro-3-hydroxy-3-(9-hydroxy-3,7-dimethylnona-1,3,5,7-tetraenyl)-4,4-dimethylthiophen (XIIIa).—The above diol (6·0 g.) in ether (300 ml.) was added dropwise with stirring to lithium aluminium hydride (3 g.) in ether (400 ml.), and the mixture was heated under reflux for 3 hr. The product was isolated in the usual way and was a yellow viscous oil (3·5 g.) which resisted all attempts at crystallisation. The oil, in benzene, was chromatographed on alumina and elution with benzene–ether (1 : 1) gave the tetraenol (0·3 g.) which separated from benzene in yellow needles, m. p. 142°. The compound rapidly became oily at 0° under nitrogen, and neither satisfactory analytical data nor crystalline derivatives could be obtained.

Perhydro-3-hydroxy-3-(3-hydroxy-3-methylocta-4,6-dien-1-ynyl)-2,4,4-trimethylthiophen (VIIIb).—3-Ethynylperhydro-2,4,4-trimethylthiophen-3-ol (3·0 g.) in ether (10 ml.) was added dropwise to ethylmagnesium bromide (from 1·1 g. of magnesium) in ether (100 ml.), and the mixture stirred for 3 hr.; some tetrahydrofuran was added to facilitate stirring. Hepta-3,5-dien-2-one (2·9 g.) in tetrahydrofuran (10 ml.) was added at 0° and stirring continued for 3 hr. at 19°. 20% Aqueous ammonium chloride was then added at 0°, and the product isolated in the usual way with ether. It was a yellow-green oil (5·7 g.) which was chromatographed on alumina from light petroleum. Elution with benzene–light petroleum (1 : 1) gave the original acetylene (1 g.), and benzene–ether (1 : 1) then gave the *methylocta-4,6-dien-1-yn-3-ol derivative* (1·94 g.), n_D^{20} 1·5355, which distilled at 60°/10^{-5} mm. as a yellow-green viscous oil, n_D^{13} 1·5388 (Found: C, 68·2; H, 8·7; S, 10·9. $C_{16}H_{24}O_2S$ requires C, 68·6; H, 8·6; S, 11·4%).

Perhydro-3-hydroxy-3-(7-hydroxy-3-methylocta-3,5-dien-1-ynyl)-2,4,4-trimethylthiophen (IXb).—The above methylocta-4,6-dien-1-yn-3-ol derivative (0·69 g.) in acetone (20 ml.) was added to 1% aqueous hydrochloric acid (10 ml.) under nitrogen and set aside at 19° for 3 hr. After neutralisation with saturated aqueous sodium hydrogen carbonate, the product was isolated with ether and obtained as a pale yellow oil (0·62 g.), n_D^{19} 1·5598. It was chromatographed on alumina, and elution with benzene–light petroleum (1 : 1) gave the substituted *methylocta-3,5-dien-1-yn-7-ol* (0·5 g.) as a pale yellow oil, b. p. 70°/10^{-5} mm., n_D^{11} 1·5560 (Found: C, 68·6; H, 8·6; S, 11·4. $C_{16}H_{24}O_2S$ requires C, 68·6; H, 8·6; S, 11·4%).

Perhydro-3-hydroxy-2,4,4-trimethyl-3-(3-methylocta-3,5-dien-1-yn-7-onyl)thiophen.—The 3,5-dien-1-yn-7-ol (IXb) (0·32 g.) in carbon tetrachloride (10 ml.) was shaken for 1 hr. with activated manganese dioxide (3 g.). The mixture was centrifuged and evaporation of the supernatant liquid gave the desired ketone as a viscous green oil (0·20 g.). The *semicarbazone* separated from aqueous methanol in colourless needles, m. p. 178—179° (Found: C, 61·2; H, 7·4; S, 12·7. $C_{17}H_{25}N_3O_2S$ requires C, 60·9; H, 7·5; S, 12·5%).

Perhydro-3-hydroxy-3-(3-hydroxy-3,7-dimethylnona-4,6,8-trien-1-ynyl)-2,4,4-trimethylthiophen (XIb).—3-Ethynylperhydro-2,4,4-trimethylthiophen-3-ol (17 g.) was treated with ethylmagnesium bromide (from 6·0 g. of magnesium), followed by 6-methylocta-3,5,7-trien-2-one (13·6 g.), the solvents and conditions being as described for the similar reaction with 3-ethynylperhydro-4,4-dimethylthiophen-3-ol. The crude *4,6,8-trien-1-yn-3-ol* (31 g.) was a red viscous oil, and a portion (8 g.) in benzene–light petroleum (1 : 1) was chromatographed on alumina. Elution with the same solvent gave the original acetylenic alcohol (1·0 g.), and benzene–ether (1 : 1) subsequently eluted the required trienyn-ol (3·8 g.), n_D^{25} 1·5599. This distilled at 70°/10^{-5} mm. giving a viscous yellow oil, n_D^{12} 1·5550 (Found: C, 70·1; H, 8·6; S, 10·4 $C_{18}H_{26}O_2S$ requires C, 70·5; H, 8·5; S, 10·5%).

Perhydro-3-hydroxy-3-(9-hydroxy-3,7-dimethylnona-3,5,7-trien-1-ynyl)-2,4,4-trimethylthiophen (XIIb).—The crude 4,6,8-trien-1-yn-3-ol (22 g.) from the previous reaction was dissolved in 90% aqueous acetone (600 ml.) containing 0·1% of sulphuric acid, and after 3 hr. at 18° was poured into water (1 l.) and extracted with ether. The alkali-washed ether extract was dried and then evaporated *in vacuo* to an orange viscous oil (21 g.). This crude diol (15 g.) was seeded in cyclohexane solution with a crystal of the pure 3,5,7-trien-1-yn-9-ol of m. p. 128—129°, obtained from the hydrolysis of the anthraquinone-2-carboxylate described below. Some of the desired diol (2·5 g.) was precipitated, and the filtrate was chromatographed in benzene on alumina. Elution with benzene–ether (1 : 1) gave a further quantity (2·6 g.).

Recrystallisation of the material, obtained by chromatography, from aqueous ethanol gave yellow needles, m. p. 141—142°, while that obtained by seeding had m. p. 128—129° and separated from benzene as a microcrystalline powder without change in m. p. Recrystallisation from aqueous ethanol, however, gave yellow needles, m. p. 141—142°. When kept at room temperature a benzene solution of the seeded material gave large yellow rhombs of the *diol*, m. p. 120°, which recrystallised under similar conditions without change in m. p. (Found:

XUM

C, 70·4; H, 8·1; S, 10·9. $C_{18}H_{28}O_2S$ requires C, 70·5; H, 8·5; S, 10·5%). Recrystallisation of this material from aqueous ethanol also gave yellow needles, m. p. 141—142°. The three forms had almost identical ultraviolet and infrared (paraffin paste) absorption characteristics, and mixtures melted between the values given for the constituents. This diol slowly gave a feeble green colour with antimony trichloride in chloroform.

The *anthraquinone-2-carboxylate* was prepared by refluxing the crude diol (6 g.) with anthraquinone-2-carbonyl chloride (3·2 g.) and pyridine (6 ml.) in benzene (50 ml.) for 45 min. Water (6 ml.) was then added, and the benzene solution was filtered, washed, dried, and evaporated. Trituration of the residue with ether gave the orange ester (1·3 g.), which crystallised from benzene. It had m. p. 172—173°, resolidified sharply at 177°, and decomposed without melting at 225° (Found: C, 73·3; H, 5·9; S, 5·8. $C_{33}H_{32}O_5S$ requires C, 73·3; H, 5·9; S, 5·9%).

The pure 3,5,7-trien-1-yn-9-ol was initially obtained by hydrolysing this ester with 2N-alcoholic potassium hydroxide at 50° for 10 min. After the solution had been filtered and poured into water the trienynol was extracted with ether; crystallisation from benzene gave very small crystals, m. p. 128—129°.

Perhydro-3-hydroxy-3-(9-hydroxy-3,7-dimethylnona-1,3,5,7-tetraenyl)-2,4,4-trimethylthiophen (XIIIb).—The previous 3,5,7-trien-1-yn-9-ol (2·1 g.) in ether was added dropwise to a stirred solution of lithium aluminium hydride (1·0 g.) in ether (150 ml.). The mixture was heated under reflux for 3 hr., cooled to 0°, and treated cautiously with ice and saturated aqueous tartaric acid. The aqueous layer was extracted with ether, and the combined ether solutions were washed with saturated aqueous tartaric acid and then water, dried, and evaporated. The residual yellow oil (1·1 g.), dissolved in benzene, was chromatographed on alumina. Elution with benzene–ether (1 : 1) gave unreduced trienynol (0·18 g.), followed by the *tetraen-9-ol* (0·43 g.), which separated from benzene in pale yellow needles, m. p. 143—144° (Found: C, 69·6; H, 8·8; S, 10·1. $C_{18}H_{30}O_2S$ requires C, 70·0; H, 9·1; S, 10·4%). The m. p. was depressed on mixture with the initial trienynol, and the compound gave a green colour with antimony trichloride in chloroform.

Acetyl chloride (0·13 g.) in ether (5 ml.) was added to the tetraen-9-ol (0·25 g.) in ether (5 ml.) and pyridine (0·04 ml.) at 0°. After 40 min. at room temperature the mixture was shaken successively with cooled N-sulphuric acid and aqueous sodium hydrogen carbonate, and then the ethereal layer was dried and evaporated. The residual *acetate* (0·06 g.) separated from benzene as colourless needles, m. p. 107—108° (Found: C, 68·3; H, 8·4; S, 9·4. $C_{20}H_{30}O_3S$ requires C, 68·6; H, 8·6; S, 9·1%).

We thank the Dow Chemical International Ltd. for a gift of distilled magnesium, Dr. A. C. Waine for a gift of methyl methacrylate, Mr. M. J. Revett for the synthesis of some 6-methylocta-3,5,7-trien-2-one, and Mr. A. O. Plunkett for some technical assistance. This work was supported by a grant from the Rockefeller Foundation to the Department of Biochemistry, University of Oxford.

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XUM

132. *Infrared Spectra of Substituted Salicylic Acids and Their Esters.*

By C. J. W. Brooks, G. Eglinton, and J. F. Morman.

The dependence of ester-carbonyl frequencies on the nature of the *O*-alkyl group is briefly discussed. Data are presented for the carbonyl and hydroxyl stretching vibrations of 21 substituted salicylic acids and their methyl esters in dilute solution (carbon tetrachloride). The effects of other solvents are examined.

Alkyl substitution in the 3- and particularly in the 6-position leads to lower carbonyl frequencies: the displacement increases with the bulk of the substituent. The carboxylic-hydroxyl stretching frequencies of the monomeric alkyl-substituted acids are all close to 3530 cm.$^{-1}$ except for the 6-substituted acids examined, in which cases they occur at 3513—3519 cm.$^{-1}$.

This paper describes infrared spectroscopic studies of a series of mono- and di-substituted salicylic acids and their methyl esters. These compounds form a convenient group for the study of environmental effects on a relatively rigid chelated system. Particular attention has been given to nuclear substitution adjacent to the chelated groups, which is known to modify certain biological actions of salicylic acid.[1] The present work appears to be the first deliberate study of the steric enhancement of chelation recently adumbrated by Hunsberger *et al.*[2]

Experimental

Materials.—Many acids were obtained commercially. The following were prepared essentially by published methods: 3-allyl-,[3] 3-propenyl-,[4] 3- and 5-isopropyl-,[5] 5-methyl-,[6] and 6-methyl-salicylic acid.[7] 3-2′-Methylallylsalicylic acid, m. p. 122°, was obtained by thermal rearrangement of *O*-2′-methylallylsalicylic acid.[8] 3-Phenylsalicylic acid was isolated from Eastman " Practical " grade of acid by dissolution in saturated aqueous sodium carbonate (*ca.* 1 equiv.), filtration, precipitation with N-hydrochloric acid (0·8 equiv.), and recrystallisation from ethylene dichloride (charcoal). Sublimation at 0·1 mm. afforded acid of m. p. 186—187·5°: its purity was confirmed by paper chromatography. *o*-Carvacrotic, 3,6-dimethylsalicylic, and 6-methyl-3-t-butylsalicylic acid were kindly supplied by Professor W. Baker, F.R.S., and Dr. W. D. Ollis; 3-t-butylsalicylic acid was generously provided by Dr. O. Fancher (Miles Laboratories, Inc.), 6-ethylsalicylic acid by Dr. R. E. Kent (Chas. Pfizer and Co. Inc.), and 3,5-di-isopropylsalicylic acid by Monsanto Ltd. Methyl esters were prepared with diazomethane: *methyl 3-t-butylsalicylate*, m. p. 47—48° (Found: C, 69·15; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%). Treatment of *O*-methoxycarbonylsalicyloyl chloride with t-butyl alcohol in pyridine afforded t-butyl *O*-methoxycarbonylsalicylate [bands at 1760 and 1720 cm.$^{-1}$; no hydroxyl absorption (liquid film)], hydrolysed by 2N-sodium hydroxide to *t-butyl salicylate*, b. p. *ca.* 180° (decomp.), n_D^{19} 1·5090 (Found: C, 68·0; H, 7·55. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·25%). Samples were carefully purified, finally by sublimation or short-path distillation at 0·1 mm. Purity of liquid samples was checked by gas–liquid chromatography as described elsewhere.[9]

Measurements.—Solvents were purified and spectroscopic determinations carried out by methods previously described.[9] Apparent integrated absorption intensities (β), where

$$\beta = \frac{1}{cl}\int \ln\left(\frac{T_0}{T}\right)_\nu d\nu$$

[1] Andrews, *Brit. J. Pharmacol.*, 1958, **13**, 419; *Biochem. J.*, 1960, **75**, 298; Lightbody and Reid, *Brit. Med. J.*, 1960, I, 1704.
[2] Hunsberger, Gutowsky, Powell, Morin, and Bandurco, *J. Amer. Chem. Soc.*, 1958, **80**, 3294.
[3] Tarbell and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 607.
[4] Claisen, *Ber.*, 1912, **45**, 3157.
[5] Croxall, Sowa, and Nieuwland, *J. Org. Chem.*, 1937, **2**, 253.
[6] Jones, *Chem. and Ind.*, 1958, 229.
[7] Eliel, Rivard, and Burgstahler, *J. Org. Chem.*, 1953, **18**, 1679.
[8] Brooks, Stafford, and Young, unpublished work.
[9] Brooks, Eglinton, and Morman, *J.*, 1961, 106.

XUM

and c = molarity, l = cell path (cm.), were determined by measurement of optical densities at 5 cm.$^{-1}$ intervals followed by application of Simpson's rule. The solvent–solvent baseline was taken as 100% transmission. For integration, the carbonyl bands were considered to extend over the following regions: acid monomer, +50 cm.$^{-1}$ from the trough between monomer and dimerd acid dimer, −50 cm.$^{-1}$ from the trough; methyl ester, + and −40 cm.$^{-1}$ from the band maximum.

TABLE 1. *Carbonyl and hydroxyl stretching absorptions of esters of benzoic, salicylic and 2,6-dihydroxybenzoic acids* (CCl_4 *solutions*).[a]

Alkyl group of ester	Benzoates			Salicylates			
	ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	ν_{OH}
Me	1730	11	900	1684	14	665	3210 ‡
Et	1724	14	690	1681	15	655	3200 ‡
Pr^n	1724	13	750	1681 ‡	16	625	3200 ‡
Pr^i	1720	11	855	1678 ‡	20	515	3190 ‡
Bu^t	1717	14	675	1674[b]	13	645	3180 ‡

2,6-Dihydroxybenzoates

Alkyl group of ester	ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	ν_{OH} (chelated)	ν_{OH} (bonded)	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a
Me	1686	14	730	(3205)[c]	3470 ‡	32	265
Et	1681	17	715	(3195)[c]	3461 ‡	40	275
Pr^n	1680	15	780	(3195)[c]	3456 ‡	30	290

‡ Unsymmetrical band; values in parentheses are approximate.
[a] Approximately 0·0015M-solutions in 0·5 cm. cells (carbonyl region) or 2·0 cm. cells (hydroxyl region). [b] Determined with the Mark II Unicam S.P. 100 (spectral slit width 4 cm.$^{-1}$ at 1650 cm.$^{-1}$). [c] Subsidiary absorption near 3160 cm.$^{-1}$.

RESULTS

Esters.—The effects of substitution in the methyl group of methyl benzoate, methyl salicylate, and methyl 2,6-dihydroxybenzoate were first examined (Table 1). The carbonyl frequency falls as the *O*-alkyl group is changed in the sequence, Me, Et, ≈Pr^n, Pr^i, Bu^t. This order appears to correspond to the inductive effects normally ascribed to these groups,[10] though in the t-butyl esters deformation of the C–CO–O bond angle may contribute to the shift. (Where t-butyl substituents actually adjoin a carbonyl function a marked decrease in frequency is noted.[11]) The centres of the broad hydroxyl bands due to the chelated phenolic groups of the salicylates and 2,6-dihydroxybenzoates show small frequency shifts paralleling the carbonyl displacements. The second phenolic group in the latter esters (I) is bonded to the alkyl-oxygen atom of the ester, and again the frequency is dependent on the *O*-alkyl group, rotation of which is restricted.

The hydroxyl and carbonyl stretching frequencies of a series of methyl esters of substituted salicylic acids are recorded in Table 2. In these compounds the conformation of the ester-carbonyl group is fixed by chelation with the phenolic hydroxyl substituent. Precise measurement of chelate hydroxyl absorption frequencies is precluded by the breadth of the bands. In the 3- and 6-substituted esters it is apparent from superposition of spectra that the band moves to lower frequencies, eventually merging into the C–H absorption region (Fig. a and Table 2). Even where the band maximum is markedly displaced, the region of absorption begins near 3500 cm.$^{-1}$: no such residual " wing " is apparent in the carbonyl absorptions, and the origin of this absorption is obscure: the minor occurrence of carbonyl overtone bands (near 3350 cm.$^{-1}$) could not account for it. The relatively weak chelation in methyl 3-hydroxy-2-naphthoate (no. 21) is reflected in the hydroxyl band at 3266 cm.$^{-1}$ (cf. ref. 12).

Methyl salicylate shows carbonyl absorption at 1684 cm.$^{-1}$ as compared with 1730 cm.$^{-1}$ for methyl benzoate and 1658 cm.$^{-1}$ for the enol form of ethyl 2-oxocyclohexanecarboxylate. Nuclear alkyl substituents not adjoining the functional groups have only minor effects on the carbonyl frequency. Substitution in the 3- and particularly in the 6-position, however, leads invariably to absorption at lower frequencies (see, *e.g.*, Fig. a), the displacement depending on the bulk of the substituent: the bands remain symmetrical in most instances and undergo

[10] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953.
[11] Maroni, *Ann. Chim.* (*France*), 1957, **2**, 757.
[12] Bergmann, Hirschberg, and Pinchas, *J.*, 1950, 2351.

little broadening. This "*ortho*-effect" is conveniently exemplified among the isomers nos. 2, 3, 5, and 13 and in the benzo-analogues 19 and 20. The data observed for esters 19, 20, and 21 are in good agreement with those of Hunsberger *et al.*[13a] A similar steric effect is apparent in methyl 10-hydroxyphenanthrene-9-carboxylate, in which the carbonyl frequency (1649 cm.$^{-1}$) [13b] is much lower than would be expected if only the double-bond character of the 9,10-linkage were considered.[14]

TABLE 2. *Carbonyl and hydroxyl stretching frequencies (cm.$^{-1}$) (CCl_4) [a] in substituted salicylic acids and methyl esters.*

		Ester		Acid			
No.	Substituents	ν_{CO}	ν_{OH} (chelate) [b]	ν_{CO} monomer	ν_{CO} dimer	ν_{OH} of CO_2H (monomer)	ν_{CO} in presence of ether (4% v/v)
1	H	1684	3210	1698	1663	3530	1679
2	4-Me	1681	3200	1697	1662 ‡	3532	1679
3	5-Me	1684	3225	1698	1664	3530	1681
4	5-Pr^i	1684	3230	1698 ‡	1665	3531	1681
5	3-Me	1681	3195	1695	1660	3531	1677
6	3-Pr^i	1679	3180	1693	1659	3531	1678
7	3-Bu^t	1676	(3110)	1691	1657	3530	1670
8	3-Allyl	1682	3185	1695	1660	3530	*
9	3-Propenyl	1682	3170	1693	1660	3529	*
10	3-2′-Methylallyl	1680	3185	1696 ‡	1659	3530	*
11	3-Phenyl	1681 ‡	3155	1695	1660	3528	1675
12	3,5-Pr$^i_2$	1677	3185	1691	1657	3531	1675
13	6-Me	1671 ‡	(3120)	1686	1650	3517	1667 (1660sh)
14	6-Et	1670	(3080)	1683	1649	3515	1665
15	3,6-Me_2	1668 ‡	(3100)	1679 ‡	1641	3518	1658 ‡
16	3-Pr^i, 6-Me	1663	(3040)	1676 ‖	1643 ‖	3518	1660
17	3-Bu^t, 6-Me	1662	(3000)	1671	1639	3519	1658
18	3-Me, 6-Pr^i	1666	(3020)	1677	1640	3514	1657 ‖
19	5,6-Benzo-	1656	(3030)	1668	1641	3513	*
20	3,4-Benzo-	1671	(3065)	1683	1650, 1635	3530	*
21	4,5-Benzo-	1692	3265	1703	1670	3527	*

* Not measured. ‡ Unsymmetrical band. ‖ Irregular contour. sh = shoulder. Values in parentheses are approximate.

[a] Esters were examined as approx. 0·0015M-solutions. The molarity of acids in carbon tetrachloride was 0·0015M (±0·00002M) except for nos. 4 (0·00127M), 19 and 21 (saturated solutions). The solutions in ether–carbon tetrachloride were 0·0015M (±0·00003M) with the exceptions of nos. 15 (0·00073M) and 17 (0·0016M). Measurements were made in 0·5 cm. cells (carbonyl region) and 2·0 cm. cells (hydroxyl region). [b] The frequency values quoted are for the band maxima reasonably attributable to this vibration mode: sharp peaks, sometimes more intense than the bands cited, in the 3000 cm.$^{-1}$ region (C–H stretching absorptions) are ignored. In nos. 7 and 13—20 the appreciable overlap of OH and CH absorptions renders the values approximate, as indicated. Apparent half-band widths ($\Delta\nu_{\frac{1}{2}}^a$) were observed as follows. Ester-carbonyl bands, 15 ± 2 cm.$^{-1}$ (except no. 7, 11 cm.$^{-1}$ and nos. 15, 16, and 18, 21 ± 2 cm.$^{-1}$). Ester-hydroxyl bands, approx. 120—570 cm.$^{-1}$, increasing generally through the series with decreasing values of ν_{OH} and ν_{CO}. Acid monomer carbonyl bands, 12 cm.$^{-1}$ (salicylic acid) to 27 cm.$^{-1}$ (no. 16) with a general trend upwards on increasing substitution. Acid dimer carbonyl bands, 15—27 cm.$^{-1}$ with no apparent regularity. Acid carbonyl bands in ether–carbon tetrachloride, 19—29 cm.$^{-1}$. Acid monomer hydroxyl bands, 35 ± 2 cm.$^{-1}$ except no. 21 (29 cm.$^{-1}$).

Frequencies, half-band widths, and intensities (ε_a) of carbonyl absorptions have been determined for some esters in several solvents. The frequency data, summarised in Table 3, show that the solvent shifts for the salicylates are only about half those observed for methyl benzoate, in accordance with the lower carbonyl basicity [9] in the chelated esters. The abnormally small shift for t-butyl salicylate in chloroform is ascribed to steric inhibition of association with the solvent. The half-band widths show some regularities: methyl 3-isopropyl-6-methylsalicylate has the broadest, methyl 3-t-butylsalicylate the narrowest, bands (*e.g.*, $\Delta\nu_{\frac{1}{2}}^a$ in hexane 16 and 7 cm.$^{-1}$ respectively). Through the sequence of solvents n-hexane, CCl_4, $CH_3{\cdot}CN$, $CHCl_3$ the half-band widths show a general increase, *e.g.*, methyl 3- and 6-methylsalicylate both have

[13] (*a*) Hunsberger, *J. Amer. Chem. Soc.*, 1950 **72**, 5626; (*b*) Hunsberger, Ketcham, and Gutowsky, *ibid.*, 1952, **74**, 4839.
[14] Bellamy and Beecher, *J.*, 1954, 4487.

XUM

$\Delta\nu_{\frac{1}{2}}$[a] 10 cm.$^{-1}$ in hexane, 23 cm.$^{-1}$ in chloroform. At the same time the intensities (ε_a) generally decrease. For carbon tetrachloride the intensities (ε_a) range from 785 (compound no. 2) to

TABLE 3. *Shifts of ester carbonyl frequencies in different solvents.*

Ester	ν_{CO} (hexane)	$\Delta\nu = \nu_{CO}$ (hexane) − ν_{CO} (solvent) CCl_4	$CH_3{\cdot}CN$	$CHCl_3$
Me benzoate	1735	5	11	15
Me salicylate	1686	2	5	7
Me 3-methylsalicylate	1682	1	4	6
Me 3-t-butylsalicylate	1678	2	5	7
Me 6-methylsalicylate	1672	1	5	6
Me 3-isopropyl-6-methylsalicylate	1666	3	7	8
Bu^t salicylate	1676	2	5	3

370 (no. 18) l. mole^{-1} cm.$^{-1}$. The trend towards lower values with 3,6-disubstitution is accompanied by band-broadening, leading to approximate constancy of integrated intensities ($10^{-4}\beta \sim 3$ l. mole^{-1} cm.$^{-2}$).

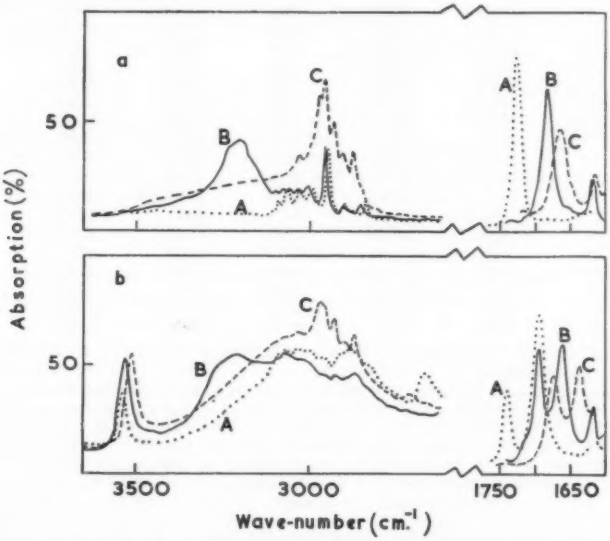


FIG. a. *Methyl esters* (0·00135M *in* CCl_4), 2 *cm. cells* (3650—2600 *cm.*$^{-1}$), 0·5 *cm. cells* (1760—1600 *cm.*$^{-1}$). A, *benzoate*; B, *salicylate*; C, 6-*isopropyl*-3-*methylsalicylate*.

FIG. b. *Acids* (0·0015M *in* CCl_4), 2 *cm. cells* (3650—2600 *cm.*$^{-1}$), 0·5 *cm. cells* (1760—1600 *cm.*$^{-1}$). A, *benzoic*; B, *salicylic*; C, 6-*isopropyl*-3-*methylsalicylic*.

Other Correlations.—In the group of methyl esters examined two intense C–H bands of the ester methyl group occur near 2950 and 2850 cm.$^{-1}$, and are most clearly seen in compounds 19—21 which lack other alkyl groups.

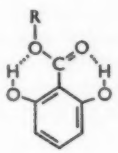
Spectra of methyl esters as liquid films or Nujol mulls will appear in the D.M.S. Index (Butterworths) as spectral cards nos. 6521 onwards. The general absorption patterns are little dependent on the bulk of the substituents; thus the 3,6-dimethyl and 6-methyl-3-t-butyl derivatives exhibit similar spectra with the principal γCH at 804 and 806 cm.$^{-1}$ respectively (cf. 1,2,3,4-tetramethylbenzene, 804 cm.$^{-1}$).[15] In the 6-isopropyl-3-methyl derivative this band is shifted to 820 cm.$^{-1}$. Methyl 6-methylsalicylate simulates the 1,2,3,4-tetrasubstituted compounds in having γCH absorption at 808 cm.$^{-1}$, whereas the 3-alkyl and 3-alkenyl esters show the expected bands near 760 cm.$^{-1}$.

[15] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn., 1958.

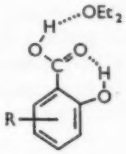
XUM

Acids.—Results recorded in Table 2 refer, with a few exceptions, to 0·0015M-solutions: at this concentration the monomeric and the dimeric species give rise to carbonyl bands of approximately equal intensity in the acids examined. The generally lower proportions of dimeric forms [1 : 1 in the salicylic acids, 2—4 : 1 in unchelated acids [9] (cf. Fig. b)] may be ascribed principally to the reduced carbonyl group basicity. The monomer carbonyl bands are displaced from those of the methyl esters by 13 cm.$^{-1}$ (S.D. 1·2), in close concordance with other substituted benzoic acids.[9,16] The frequency separation between the monomer and the dimer bands (35 cm.$^{-1}$; S.D. 2), however, is significantly lower than that (45 cm.$^{-1}$; S.D. 1·6) observed for unchelated acids. The relatively smaller shift accompanying dimer formation also reflects the lower basicity of the salicylic acid carbonyl group. In the group of acids examined in solutions containing ether, the frequency displacements (−18 cm.$^{-1}$; S.D. 2·5) accompanying formation of the ether-bonded monomers (II) correspond to the value observed for benzoic acid.[9] The concentrations of ether required to eliminate dimer absorption are generally lower than for the benzoic acids, as already noted by Forbes and Knight for ultraviolet absorption.[17] In pure ether (0·5 mm. cells) salicylic acid showed only the band attributed to form (II; R = H): there was no indication of any opening of the chelate ring. The effects of nuclear substitution on the acid-carbonyl frequencies are closely parallel to those described for the methyl ester bands.

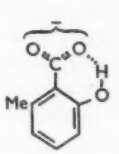
The broad band near 3200 cm.$^{-1}$ due to the chelated phenolic hydroxyl group,[18] and somewhat obscured by the absorption of the acid dimer, is detectable in salicylic acid. It becomes less well defined in the alkyl-substituted acids and is not discernible in no. 17, where it has presumably moved into the C–H absorption region. (Apart from this detail, all the 6-alkyl-acids show similar band outlines between 3600 and 2600 cm.$^{-1}$.) The hydroxyl group of the monomeric acid exhibits a sharp band at a position (3530 ± 3 cm.$^{-1}$) virtually independent of alkyl-substitution at the 3-, 4-, and 5-position but occurring at a lower frequency (3513—3519 cm.$^{-1}$) in all the 6-alkyl-acids examined, and in the naphthoic analogue (no. 19). This feature may have diagnostic value, not merely to locate a 6-substituent, but also to distinguish its type, since within the small group studied the frequency displacement parallels the bulk of the 6-alkyl group.



(I)



(II)



(III)

Apparent extinction coefficients and integrated intensities of the carbonyl absorptions have been measured. The sensitivity of the monomer–dimer equilibrium to minor changes in concentration precludes correlations [19] with pK's within the narrow range of acid strengths represented here. It is sufficient to note that for the acids nos. 1—12, without 6-substituents, the mean value of $\varepsilon_{monomer}/\varepsilon_{dimer}$ is 1·0 (S.D. 0·1) while for the 6-alkylsalicylic acids (nos. 13—18) known or expected to have slightly higher pK's (*e.g.*, no. 13, 3·32; [20] no. 14, *ca.* 3·7,[21]) the ratio is 0·86 (S.D. 0·04). The more marked effect of a greater change in pK is exemplified by 6-chlorosalicylic acid (pK 2·63 [20]) for which the ratio in 0·0015M-solution is 2·0. The ratios of integrated intensities are less reliable, particularly for the 6-substituted acids, in which the displaced dimer bands are close to the region of aromatic C=C stretching absorption (near 1610 cm.$^{-1}$) and may be affected by Fermi resonance. Moreover, the dividing line between the monomer and the dimer bands is difficult to assign with precision. The intensities (ε_a ranging from 575 to 370) observed for the bonded monomeric acids in ether–carbon tetrachloride show a trend similar to, but less well-defined than, that observed for the methyl esters in carbon tetrachloride.

[16] Peltier, Pichevin, Dizabo, and Josien, *Compt. rend.*, 1959, **248**, 1148.
[17] Forbes and Knight, *Canad. J. Chem.*, 1959, **37**, 334.
[18] Martin, *Nature*, 1950, **166**, 474.
[19] Allen and Caldin, *Quart. Rev.*, 1953, **7**, 255.
[20] Bray, Dippy, Hughes, and Laxton, *J.*, 1957, 2405.
[21] Pasternack, Conover, Bavley, Hochstein, Hess, and Brunings, *J. Amer. Chem. Soc.*, 1952, **74**, 1928.

Discussion

The principal feature of the results is the effect of 3- and 6-alkyl substitution. The uniformity of the frequency shifts in the three regions of absorption associated with ester, acid monomer, and acid dimer suggests that the bands are not seriously perturbed by vibrational interaction. The lower frequencies found for 3-alkylsalicylates (nos. 5—7; cf. also nos. 8—11) may be partly due to inductive effects (cf. the shifts of 2 cm.$^{-1}$ on *meta*-methylation of benzoic acid) [9,16] although it should be noted that an opposite effect would ensue from the expected [22a] increase in electron density at the phenolic oxygen atom. The more marked shifts caused by the bulkier 3-alkyl groups are ascribed to the steric enhancement of chelation [2] by compression of the phenolic hydroxyl group, probably with reduction in the O–H · · · O distance. (Similarly, bulky 6-, but not 4-, alkyl substituents strengthen the intramolecular hydrogen bond in substituted 2-bromophenols.[23]) The more striking displacements seen in 6-alkylsalicylates presumably arise from the larger steric requirement of the carboxyl group.

It is difficult to assess from the present work the extent to which the coplanarity of the carboxyl and the phenolic hydroxyl group with the nucleus is disturbed by 3- and 6-substituents. From models it appears that some distortion would occur in all the 6-alkyl derivatives, but there is considerable uncertainty regarding the effective " interference radii " (cf. the apparent coplanarity of the substituents in 1,4-dibromo-2,5-di-t-butylbenzene [22b]). Ultraviolet absorption data are not very informative. Thus, as pointed out by Burawoy *et al.*,[24] the formation of an intramolecular hydrogen bond has little influence on the absorption: salicylic acid and *m*-hydroxybenzoic acid exhibit closely similar spectra in ethanol.[25] Moreover, the introduction of a 6-methyl group causes only a small displacement of the band near 240 mμ, with no appreciable reduction in intensity. Similar small effects are found in the 3,6-dialkylsalicylates: only *o*-carvacrotic acid (no. 18), among those examined, shows an indication of possible steric inhibition of conjugation in the reduced intensities of both the 246 and the 316 mμ absorption.[26] Comparison of carbonyl frequencies for this compound and the 3,6-dimethyl analogue (no. 15) suggests that the limit of steric enhancement of intramolecular hydrogen bonding by 6-alkylation has been reached: it would be desirable to examine a 6-t-butyl-substituted acid. More direct evidence as to coplanarity in these compounds (*e.g.*, from *X*-ray measurements) is required.

Peltier [27] and Dippy and his collaborators [20] have drawn attention to the lower acidity of 6-methylsalicylic acid (pK_a 3·32) than of salicylic acid (pK_a 3·00); the latter authors have ascribed this to inhibition of intramolecular hydrogen bonding. This view does not necessarily conflict with the infrared data, which refer to the undissociated acid; in the (solvated) resonance-stabilised anion (III) small deviations from coplanarity could lead to relative destabilisation with consequent weakening of the acid.

The essentially steric basis of the effects of *ortho*-substitution in benzoic acids is well established (cf. refs. 28, 29): the pK's of *o*-chloro- and *o*-nitro-benzoic acid are respectively 0·9 and 1·3 units lower than those of their *meta*-isomers. That steric effects predominate in 6-substituted salicylic acids is supported by the weakness of 6-chloro- and 6-nitrosalicylic acid, which approximate in strength to their 5-isomers.[20] Moreover, the carbonyl frequency in 6-chlorosalicylic acid is at 1686 cm.$^{-1}$ (monomer), close to that of the 6-methyl

[22] " Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York, 1955: (*a*) Brown, McDaniel, and Häfliger, Chapter 14; (*b*) Sutton, Chapter 9.
[23] Brown, Eglinton, and Martin-Smith, unpublished work.
[24] Burawoy and Burawoy, *J.*, 1936, 38; Burawoy and Chamberlain, *J.*, 1952, 2310.
[25] Moser and Kohlenberg, *J.*, 1951, 804.
[26] Brooks, unpublished results.
[27] Peltier, *Compt. rend.*, 1955, 58.
[28] Crawford, *Nature*, 1950, **165**, 728; Ross, *J. Amer. Chem. Soc.*, 1948, **70**, 4039; McDaniel and Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 3756.
[29] Dippy, Hughes, and Bray, *J.*, 1959, 1717.

XUM

analogue despite the different polar character of the substituents. Two hydroxyl bands are observed for 6-chlorosalicylic acid; the first (3508 cm.$^{-1}$) is ascribed to the monomer carboxylic free hydroxyl and the second, weaker absorption (3431 cm.$^{-1}$) to a hydrogen-bonded species. Such bonding is not observed in *o*-halogenobenzoic acids and is attributed to the conformational rigidity imposed by the salicylate chelation.[9]

We thank Professor R. A. Raphael and Dr. J. Reid for their interest, Dr. L. J. Bellamy for his comments, Miss I. F. Currie for preparing several samples, and Mrs. F. Lawrie for some measurements.

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133. *The Synthesis of Chelating Agents Related to Cyclohexane-1,2-diamine-*NNN′N′*-tetra-acetic Acid.*

By R. Belcher, W. Hoyle, and T. S. West.

trans-Cyclopentane-1,2-diamine-*NNN′N′*-, 4-methylcyclohexane-*trans* *-1,2-diamine-*NNN′N′*-, and *trans* *-cycloheptane-1,2-diamine-*NNN′N′*-tetra-acetic acid have been synthesised from the corresponding *vic*-dioximes *via* the *vic*-diamines. The new complexans have been prepared as potential analytical reagents; they possess some interesting properties which may prove of value.

Since the introduction by Schwarzenbach and Ackermann [1] of ethylenediamine-*NNN′N′*-tetra-acetic acid (EDTA) as an analytical complex-forming reagent of outstanding importance there has been an increasing search for similar reagents with more selective or more desirable physical properties. The report [2] of the high chelating power of *trans*-cyclohexane-1,2-diamine-*NNN′N′*-tetra-acetic acid (CDTA) and the prediction [3] that the cyclopentane homologue should have even greater power led to our synthesising the compounds described below.

Analogues of EDTA are best prepared by reaction of the diamine with chloroacetic acid [4] or by condensation of the diamine with formaldehyde and hydrogen cyanide followed by hydrolysis of the tetra-nitrile.[5] The diamines are conveniently prepared by reduction of the corresponding *vic*-dioximes which in turn are prepared from the readily available monoketones.[6]

Jaeger and Blumendal [7] reduced cyclopentane-1,2-dione dioxime with sodium and ethanol and obtained *trans*-cyclopentane-1,2-diamine. We have used the same method for the preparation of 4-methylcyclohexane-1,2-diamine and cycloheptane-1,2-diamine and therefore we assume that the amine groups have the *trans*-configuration. Condensation of chloroacetic acid with both *cis*- and *trans*-cyclohexane-1,2-diamine failed to give the *cis*-tetra-acetic acid derivative, but readily afforded the *trans*-tetra-acetic acid derivative.[8] The ease with which the following tetra-acetic acid derivatives were synthesised is adduced

* The configuration of these diamines is not known, but for reasons given in the text the *trans*-configuration is strongly indicated.

[1] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798.
[2] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1949, **32**, 1682.
[3] Martell and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice Hall, New York, 1952, p. 180.
[4] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1948, **31**, 1029.
[5] B.P. 651,990.
[6] Belcher, Hoyle, and West, *J.*, 1958, 2743.
[7] Jaeger and Blumendal, *Z. anorg. Chem.*, 1928, **175**, 164.
[8] Hoyle, Ph.D. Thesis, University of Birmingham, 1959.

XUM

to confirm their *trans*-configuration though in no case was this point investigated experimentally.

trans-Cyclopentane-1,2-diamine was easily converted into *trans*-cyclopentane-1,2-diamine-*NNN'N'*-tetra-acetic acid (CPDTA) by condensation with chloroacetic acid. CPDTA was found to be insoluble in all common solvents except formamide, and was purified by repeated precipitation from alkaline solution with acid. The rigidity of the cyclopentane ring and the symmetry of the molecule may account for this very poor solubility compared with that of the higher homologues.

4-Methylcyclohexane-*trans*-1,2-diamine was prepared by reduction as mentioned above, and isolated as the hydrogen sulphate, since the hydrochloride is very deliquescent. Though the diamine has been reported [9] no derivatives were recorded; we characterised the diamine as the dibenzoyl derivative and picrate. Condensation of the diamine with chloroacetic acid gave a poor yield (*ca.* 30%) of 4-methylcyclohexane-*trans*-1,2-diamine-*NNN'N'*-tetra-acetic acid (MCDTA) which could not be isolated from the mother-liquor.[10] Because of the small quantities of materials involved, the complicated distillation procedure of Schwarzenbach *et al.*[4] was not attempted, but a method using the intermediate formation of the tetra-nitrile was adopted. Hydrolysis of the tetra-nitrile with sulphuric acid and with sodium hydroxide was incomplete; barium hydroxide solution proved more satisfactory,[11] though some difficulty was experienced in obtaining the acid from solution owing to its tendency to form syrups. The high solubility of this compound in water and in ethanol may be due to the lack of symmetry of the molecule.

trans-Cycloheptane-1,2-diamine was prepared by reduction of the dioxime and was isolated as the hydrochloride. The literature of this compound lists no derivatives.[12] Treatment of the diamine with chloroacetic acid gave *trans*-cycloheptane-1,2-diamine-*NNN'N'*-tetra-acetic acid (CHDTA) which was isolated by acidification of the mother-liquor. Careful acidification of a solution of the tetrapotassium salt gave a precipitate which had the composition of a monopotassium derivative and could be crystallised to constant melting point. The formation of a monoalkali derivative of a complexan is interesting: it is thought that the compound is a salt and not a chelate, but as yet no further investigation has been made.

The complexans described possess several unusual properties which may prove of value in applications to specific problems. There are considerable differences in their solubilities: CPDTA is insoluble in most solvents, whereas MCDTA is appreciably soluble in water and ethanol. No increase in selectivity has been observed but under certain conditions of pH some increase of chelating power has been noticed with CHDTA. The increasing half-wave potential of the polarographic reduction wave of the copper and cadmium chelate waves shows that the chelating power increases in the order CPDTA $<$ CDTA $\leqslant$ MCDTA $<$ CHDTA. The polarographic data [13] are supported by the potentiometric titration curves,[8] and the order of chelation is confirmed by the ability of all the complexans but CPDTA to inhibit the precipitation of cobalt and manganese sulphides in the presence of calcium ions.[10]

Experimental

trans-*Cyclopentane-1,2-diamine*.—Crude cyclopentane-1,2-dione dioxime [6] was reduced with sodium and ethanol by Jaeger and Blumendal's method.[7] The diamine was isolated by steam-distillation and the dihydrochloride was obtained by evaporation of the acidified distillate under reduced pressure. The crude residue was washed with ethanol and trans-*cyclopentane-1,2-diamine dihydrochloride* was obtained as a white powder, m. p. 315—320° (decomp.), in 70% yield (Found: C, 35·1; H, 8·1; N, 16·2. $C_5H_{14}N_2Cl_2$ requires C, 34·7; H, 8·2; N, 16·2%).

[9] Jaeger and Van Dijk, *Proc. Acad. Sci. Amsterdam*, 1936, **39**, 384.
[10] Hoyle, M.Sc. Thesis, University of Birmingham, 1957.
[11] Schwarzenbach, Senn, and Anderegg, *Helv. Chim. Acta*, 1957, **40**, 1886
[12] Bertsch, Fernelius, and Block, *J. Phys. Chem.*, 1958, **62**, 444.
[13] Hoyle and West, *Talanta*, 1959, **2**, 158.

XUM

trans-*Cyclopentane-1,2-diamine-NNN'N'-tetra-acetic Acid.*—A solution of chloroacetic acid (11·6 g.) in water (20 ml.) was neutralised with part of a solution of sodium hydroxide (12 g.) in water (20 ml.), the temperature being kept below 20°. *trans*-Cyclopentane-1,2-diamine dihydrochloride (4·7 g.) was added to the solution of sodium chloroacetate, then sufficient sodium hydroxide solution to liberate the free amine. The temperature of the solution was raised to 40° and maintained while one-half of the residual sodium hydroxide solution was added dropwise from the burette during 2½ hr. The other half of the sodium hydroxide solution was added during a further 2½ hr., with the temperature of the reaction mixture at 60°. The temperature was then raised to 90—100° and maintained thereat for 1 hr. The mixture was filtered and acidified at 0° to *ca.* pH 2 by addition of concentrated hydrochloric acid. The colourless crystals formed were removed and purified by repeated precipitation with hydrochloric acid from solutions of the sodium salt treated with charcoal. Colourless crystals of trans-*cyclopentane-1,2-diamine-NNN'N'-tetra-acetic acid* (CPDTA) were obtained, (5·7 g., 63%), which after drying *in vacuo* decomposed at *ca.* 250° (Found: C, 46·7; H, 5·7; N, 8·5. $C_{13}H_{20}N_2O_8$ requires C, 47·0; H, 6·1; N, 8·4%). Assay by complexometric titration 99—100%.

4-*Methylcyclohexane*-trans-1,2-*diamine.*—4-Methylcyclohexane-1,2-dione dioxime (10 g.) was reduced in ethanol solution (340 ml.) by sodium (61 g.) (cf. Jaeger and Blumendal [7]). The diamine was isolated by steam-distillation and converted into the di(hydrogen sulphate). Evaporation of the distillate under reduced pressure yielded a pink residue of crude 4-methylcyclohexane-*trans*-1,2-diamine di(hydrogen sulphate) (11·4 g., 78%). A white product was obtained by washing the crude salt with ethanol. The salt led to a *dibenzoyl derivative*, m. p. 315—316° (from ethanol) (Found: C, 75·2; H, 7·1; N, 8·1. $C_{21}H_{24}N_2O_2$ requires C, 75·0; H, 7·2; N, 8·3%), and a *picrate* (obtained by very slow crystallisation from water), m. p. 221° (decomp.) (Found: C, 39·1; H, 3·7. $C_{19}H_{22}N_8O_{14}$ requires C, 38·9; H, 3·8%).

4-*Methylcyclohexane*-trans-1,2-*diamine*-NNN'N'-*tetra-acetonitrile.*—To 4-methylcyclohexane-*trans*-1,2-diamine di(hydrogen sulphate) (10 g.) were added water (10 ml.) and concentrated sulphuric acid (9·55 g.). The solution was cooled to <20° and 36% aqueous formaldehyde (16·2 ml.) was then added. 15 Ml. of 30% w/v aqueous solution of sodium cyanide were added dropwise to the stirred reaction liquor at 20° during 3 hr. The remainder of the cyanide solution (17 ml.) was added during 3 hr. at 30°. The mixture was then heated to 35° in 1 hr. and to 50° in a further ¾ hr. The whole was allowed to cool and set aside at room temperature for 15 hr., then warmed to 40° to dissolve most of the sodium sulphate. The light brown product was removed by filtration. A single recrystallisation from methanol gave off-white crystals, m. p. 131—133° (4·0 g., 32%). 4-*Methylcyclohexane*-trans-1,2-*diamine*-NNN'N'-*tetra-acetonitrile* was obtained as colourless crystals, m. p. 133—134°, from methanol (Found: C, 63·4; H, 7·1; N, 29·6. $C_{15}H_{20}N_6$ requires C, 63·4; H, 7·1; N, 29·6%).

4-*Methylcyclohexane*-trans-1,2-*diamine*-NNN'N'-*tetra-acetic Acid.*—To hydrated barium hydroxide (6·31 g.), dissolved in water (50 ml.), 4-methylcyclohexane-*trans*-1,2-diamine-*NNN'N'*-tetra-acetonitrile (1·42 g.) was added. The mixture was boiled gently for 4½ hr. and the volume was maintained by addition of water. The barium was precipitated by the calculated amount of 10% sulphuric acid and removed. The filtrate was evaporated to low bulk, the syrup which had been formed deposited off-white crystals slowly. 4-*Methylcyclohexane*-trans-1,2-*diamine*-NNN'N'-*tetra-acetic acid* (MCDTA) was obtained as colourless crystals (from aqueous ethanol), m. p. 177° (decomp.) (0·36 g., 20%) (Found: C, 44·6; H, 7·3; N, 6·8. $C_{15}H_{24}N_2O_8.2\frac{1}{2}H_2O$ requires C, 44·45; H, 7·2; N, 6·9%).

trans-*Cycloheptane-1,2-diamine.*—*trans*-Cycloheptane-1,2-diamine dihydrochloride was obtained by reduction of cycloheptane-1,2-dione dioxime (10 g.) by the method described above for 4-methylcyclohexane-*trans*-1,2-diamine. The light-brown hygroscopic *dihydrochloride* (8·5 g., 68%) was purified from ethanolic solution, with ether, as a flocculent precipitate, m. p. 245—265° (decomp.) (Found: C, 42·2; H, 9·0; N, 14·0. $C_7H_{18}N_2Cl_2$ requires C, 41·8; H, 9·0; N, 13·9%). This led to a *dibenzoyl derivative*, m. p. 340—341° (decomp.; sealed tube) (from pyridine) (Found: C, 74·6; H, 7·2; N, 8·6. $C_{21}H_{24}N_2O_2$ requires C, 75·0; H, 7·2; N, 8·3%).

trans-*Cycloheptane-1,2-diamine-NNN'N'-tetra-acetic Acid.*—Chloroacetic acid (17·9 g.) in water (35 ml.) was condensed with *trans*-cycloheptane-1,2-diamine dihydrochloride (8·5 g.) in the presence of sodium hydroxide (18·7 g., total) as described for the preparation of CPDTA. The sodium hydroxide was added in two periods of 3 hr. each at 40° and 60° respectively. The reaction was completed as before; and the liquor was filtered to remove a brown contaminant.

XUM

Colourless crystals were deposited on acidification of the mother-liquor to pH <2 with concentrated hydrochloric acid, and after recrystallisation from water trans-*cycloheptane*-1,2-*diamine*-NNN'N'-*tetra-acetic acid* (CHDTA) was obtained (4·8 g., 31%). Dehydration *in vacuo* at 140° gave pure CHDTA as a white powder, m. p. 181—182° (decomp.) (Found: C, 49·8; H, 6·5; N, 7·7. $C_{15}H_{24}N_2O_8$ requires C, 50·0; H, 6·7; N, 7·8%).

This acid was dissolved in potassium hydroxide solution and then carefully acidified with concentrated hydrochloric acid to pH *ca.* 2. A white precipitate was obtained which, readily recrystallised from water, had m. p. 264—266° (Found: H, 6·1; N, 6·9. $C_{15}H_{22}KN_2O_8$ requires H, 5·8; N, 7·0%). Assay by complexometric titration gave 99—100% purity.

We thank the Geigy Co. Ltd. for samples of *cis*- and *trans*-cyclohexane-1,2-diamine, and one of us (W. H.) is further indebted to them for the award of a scholarship.

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134. *Olefinic Additions with Asymmetric Reactants. Part VI.*[1] *Dissymmetric Hydrogenation of (±)-4-Phenylpent-3-en-2-ol.*

By C. L. ARCUS and T. J. HOWARD.

Catalytic hydrogenation of (±)-4-phenylpent-3-en-2-ol gave the diastereoisomeric racemates of (±)-4-phenylpentan-2-ol in ratios, determined by vapour-phase chromatography, which indicate that (i) 50, (ii) 57% dissymmetric reaction (" asymmetric synthesis ") occurs during the reduction. The phenylpentanols, on removal of asymmetry at $C_{(3)}$ by oxidation, yielded (±)-4-phenylpentan-2-one, found chromatographically to be a single entity. The stereochemistry of the hydrogenation is discussed.

THERE have been described two partial asymmetric syntheses in which an allyl alcohol of type (I), on hydrogenation with Raney nickel catalyst, formed diastereoisomeric alcohols (II), which on oxidation yielded ketone (III). In the first example[2] (R = Et, R' = Pr^n), (−)-3-ethylhept-3-en-2-ol gave (−)-3-ethylheptan-2-ol, and thence (+)-3-ethylheptan-2-one; in the second[1] (R = Me, R' = Ph) (−)-3-methyl-4-phenylbut-3-en-2-ol gave (+)-3-methyl-4-phenylbutan-2-ol, which yielded (−)-3-methyl-4-phenylbutan-2-one. A new centre of asymmetry is formed at $C_{(3)}$ in these reactions, with preponderance of one configuration, as shown by the optical activity of the ketone obtained when the originally asymmetric centre $C_{(2)}$ is rendered symmetrical.

$$\underset{\text{(I)}}{CH_3{\cdot}\overset{*}{C}H(OH){\cdot}CR{:}CHR'} \longrightarrow \underset{\text{(II)}}{CH_3{\cdot}\overset{*}{C}H(OH){\cdot}\overset{*}{C}HR{\cdot}CH_2R'} \longrightarrow \underset{\text{(III)}}{CH_3{\cdot}CO{\cdot}\overset{*}{C}HR{\cdot}CH_2R'}$$

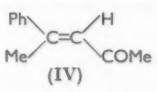
In the second example, the alcohol (II) and the ketone (III) were examined by vapour-phase chromatography. The former was found to consist of two diastereoisomers, present in unequal amounts, while the latter behaved as a single entity. These findings accord with the results based on optical activity: that hydrogenation is dissymmetric, yielding unequal amounts of the diastereoisomeric saturated alcohols, which, when oxidised together, yield a mixture of (+)- and (−)-ketone; optical isomers would not be expected to separate on a symmetrical chromatographic medium. The point was made that, where it is practicable, the quantitative estimation of diastereoisomers by vapour-phase chromatography is probably the most satisfactory method of determining product ratios in reactions of the type:

$$\left\{\begin{matrix} dX\text{-}sym Y \\ lX\text{-}sym Y \end{matrix}\right\} \longrightarrow \left\{\begin{matrix} dX\text{-}dZ \\ lX\text{-}lZ \end{matrix}\right\} + \left\{\begin{matrix} dX\text{-}lZ \\ lX\text{-}dZ \end{matrix}\right\}$$

[1] Part V, Arcus, Cort, Howard, and Le Ba Loc, *J.*, 1960, 1195.
[2] Arcus and Smyth, *J.*, 1955, 34.

The method is applicable to the inactive compounds, as indicated, and to either of the optically active series represented by one line of the above reaction. In the first instance the entities separated are the diastereoisomeric racemates shown in the braces; with an optically active initial compound, the diastereoisomers of one or other line are separated.

Vapour-phase chromatography has now been used to assess the percentage of dissymmetry in the hydrogenation of (±)-4-phenylpent-3-en-2-ol. Johnson and Kon [3] prepared 4-phenylpent-3-en-2-one by the action of methylzinc iodide on β-methylcinnamoyl chloride; it has also been obtained by the pyrolysis of 3-acetyl-4-phenylpyrazoline,[4] and by hydrolysis of 2-ethoxy-4-phenylpenta-1,3-diene.[5] It has now been prepared by the reaction of β-methylcinnamoyl chloride with dimethylcadmium, and formed needles, m. p. 38°. Johnson and Kon, who isolated the ketone by formation and hydrolysis of the semicarbazone, report it as plates, m. p. 100°; the other authors [4,5] obtained it as an oil. The structure of the present 4-phenylpent-3-en-2-one has been verified by haloform degradation, which gave β-methylcinnamic acid, m. p. 99—100°, demonstrated by Stoermer and his co-workers [6] to be the isomer having the phenyl *trans* to the carboxyl group; the ketone is accordingly assigned structure (IV).



(IV)

On reduction with aluminium isopropoxide it gave (±)-4-phenylpent-3-en-2-ol, a crystalline solid which yielded an *N*-1-naphthyl- and an *N*-4-biphenylyl-carbamate. Each of the three compounds behaved as a single entity. The alcohol is concluded to be a single geometrical isomer, and of the *trans*-configuration (V) unaltered from that of the ketone.

It was hydrogenated (in solution in ethanol, with W-3 Raney nickel catalyst,[7] the maximum temperature and pressure being 52° and 107 atm.) to (±)-4-phenylpentan-2-ol. Oxidation of this alcohol with chromic anhydride in acetic acid yielded (±)-4-phenylpentan-2-one. The vapour-phase chromatogram of the 4-phenylpentan-2-ol showed two adjacent peaks, which are ascribed to the two diastereoisomeric racemates; the less volatile isomer formed the larger peak. The chromatogram of the 4-phenylpentan-2-one showed a single peak.

Hydrogenation, oxidation, and chromatography were repeated with results closely similar to the above.

The term " percentage asymmetric synthesis " is somewhat unsuitable when applied to reactions with optically inactive compounds, and it is proposed to replace it, in this connection, by " percentage dissymmetric reaction." Where a and b are the quantities of the diastereoisomers formed, to which the areas under the corresponding peaks of the chromatogram are equivalent, the percentage dissymmetric reaction is given by $100(a - b)/(a + b)$.

The specimens of (±)-4-phenylpentan-2-ol were redistilled without the use of a column, in order to effect purification without appreciable separation of the diastereoisomers by fractionation. Dissymmetric reaction was found for the main fractions from the two hydrogenations to be 50% and 57%. The low- and the high-boiling fraction from the first hydrogenation, comprising respectively 6 and 11% of the product, gave chromatograms indicating 43% and 53% of dissymmetric reaction, whence the degree of fractionation was slight and the percentages of dissymmetric reaction derived from the main fractions are concluded to be substantially correct.

The following have been inferred in earlier discussions,[2,1] and are considered applicable to the present work: (*a*) The addition of hydrogen is *cis* to that surface of the molecule which is adjacent to the nickel surface. (*b*) No dissymmetric reaction could result if adsorption, and hence hydrogenation, were to occur with equal ease at either side of the

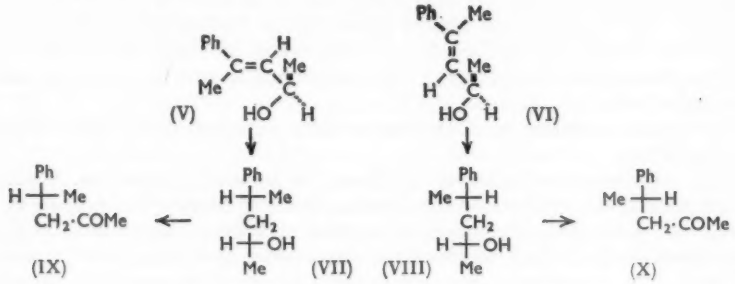
[3] Johnson and Kon, *J.*, 1926, 2748.
[4] Howard and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 165.
[5] Martin and Normant, *Bull. Soc. chim. France*, 1957, 432.
[6] Stoermer, Grimm, and Laage, *Ber.*, 1917, **50**, 959; Stoermer and Laage, *ibid.*, p. 981.
[7] Pavlic and Adams, *J. Amer. Chem. Soc.*, 1946, **68**, 1471.

double bond; hence the asymmetric carbon atom must determine the conformation in which the molecule is adsorbed, dissymmetric adsorption preceding, and leading to, dissymmetric hydrogenation. (*c*) The side of the molecule which becomes adjacent to the nickel surface is that which conforms most closely to a plane. (*d*) The oxygen lone-pair(s) and the π-electrons of the unsaturated alcohol interact with the nickel surface.

Two conformations (V) and (VI) are available which, equally, place the methylphenylethylenic part of the molecule and the oxygen atom close to the plane of the paper.

Hydrogenation of form (V), from below the plane of the paper, would produce the phenylpentanol (VII), and of form (VI) the diastereoisomer (VIII). On oxidation, isomers (VII) and (VIII) would yield the enantiomeric ketones (IX) and (X). However, each of the formulæ (V—X) should be accompanied by its enantiomer, since reaction is of the (±)-4-phenylpent-3-en-2-ol; hence formulæ (VII) and (VIII) represent the diastereoisomeric racemates of 4-phenylpentan-2-ol, and both ketones (IX) and (X) represent racemic 4-phenylpentan-2-one. The last result is in accord with the finding that the ketone behaved as a single entity during vapour-phase chromatography.

The percentages of dissymmetric reaction found (i, 50; ii, 57%) correspond to formation of the diastereoisomeric racemates in ratio (i) 3·02, (ii) 3·65 : 1, whence the appropriate adsorption-conformations were effective in these ratios. In an attempt to identify the more favoured conformation, C.R.L.-Catalin models of forms (V) and (VI) were examined; these show that the methyl groups are more widely separated in (V) than in (VI), but that hindrance between the oxygen atom and the methyl group [$C_{(5)}$] is appreciable in (V) and absent in (VI). It is therefore difficult, from the data at present available, to select one conformation as certainly more probable than the other.



Experimental

M. p.s are corrected.

β-Methylcinnamic acid [3] (m. p. 99—100°; 154 g.) was warmed for 1½ hr. with thionyl chloride (170 g.); excess of the latter was removed under reduced pressure and the product distilled. It gave β-methylcinnamoyl chloride (161 g.), b. p. 148°/22 mm.

To a boiling solution of dimethylcadmium [3] (from methyl bromide 175 g., magnesium 42·5 g., and cadmium chloride 181 g.) in benzene (750 ml.); β-methylcinnamoyl chloride (161 g.) in benzene (200 ml.) was so added that gentle refluxing was maintained; then stirring and heating were continued for another hour (a powerful stirrer was used because a heavy sludge was formed in the course of reaction). To the cooled mixture ice (1 kg.), then excess of 3N-sulphuric acid, were added; the benzene layer was separated and the aqueous layer extracted with benzene (2 × 200 ml.). The combined benzene solutions were washed with water, 5% sodium carbonate solution (300 ml.), water, and saturated brine, dried (Na_2SO_4), and evaporated. The product gave on distillation a yellow oil (90 g.), b. p. 127—130°/12 mm., n_D^{25} 1·5675, which on being chilled crystallised. The solid was collected and recrystallised from light petroleum (b. p. 60—80°), yielding 4-phenylpent-3-en-2-one (71 g.), pale yellow needles, m. p. 37·5—38·5° (Found: C, 82·55; H, 7·6. Calc. for $C_{11}H_{12}O$: C, 82·45; H, 7·55%). The semicarbazone

[3] *Org. Synth.*, **38**, 41; **28**, 76.

was recrystallised from aqueous ethanol and had m. p. 193·5—194·5°; the 2,4-dinitrophenylhydrazone, recrystallised from methanol, had m. p. 193·5—194° (Found: C, 59·5; H, 4·85; N, 16·7. Calc. for $C_{17}H_{16}N_4O_4$: C, 60·0; H, 4·75; N, 16·45%). Because the m. p. of this ketone is similar to that of the isomeric 3-methyl-4-phenylbut-3-en-2-one (38° [1]), specimens of the ketones were mixed; the mixture melted immediately.

4-Phenylpent-3-en-2-one (1·0 g.) was added to a solution of sodium hydroxide (3·0 g.) and aqueous sodium hypochlorite (10%) (27 ml.) in water (73 ml.). The whole was heated under reflux for 40 min., then saturated with sulphur dioxide. The product was filtered off, washed with water, and twice recrystallised from light petroleum (b. p. 100—120°); it had m. p. 99—100° alone and when mixed with β-methylcinnamic acid.

4-Phenylpent-3-en-2-one (26 g.) was heated for 1 hr. with a solution of aluminium isopropoxide (from aluminium 10 g., and propan-2-ol 200 ml.), the acetone formed being slowly distilled. The propan-2-ol was then distilled under reduced pressure and the cooled product added to an excess of 3N-sulphuric acid and ice. The solid alcohol which separated was dissolved in ether, and the solution was washed with 3N-sulphuric acid, 2N-sodium hydroxide, and water, and dried (K_2CO_3), and the ether distilled. The product was recrystallised from light petroleum (b. p. 100—120°) and yielded (±)-4-*phenylpent-3-en-2-ol* (17 g.), plates, m. p. 63—64°, n_D^{25} 1·5521 (supercooled) (Found: C, 81·5; H, 8·85. $C_{11}H_{14}O$ requires C, 81·45; H, 8·7%). (±)-1-*Methyl-3-phenylbut-2-enyl* N-1-*naphthylcarbamate*, recrystallised from light petroleum (b. p. 100—120°), had m. p. 96—97° (Found: C, 79·4; H, 6·15; N, 4·35. $C_{22}H_{21}NO_2$ requires C, 79·7; H, 6·4; N, 4·25%); the N-4-*biphenylylcarbamate*, similarly recrystallised, had m. p. 116·5—117° (Found: C, 80·1; H, 6·7; N, 4·1. $C_{24}H_{23}NO_2$ requires C, 80·65; H, 6·5; N, 3·9%).

(±)-4-Phenylpent-3-en-2-ol (15·0 g.), in solution in 99% ethanol (75 ml.), was hydrogenated in the presence of W-3 Raney nickel (1 g.); the total time was 8 hr. 50 min., and the maximum temperature and pressure attained were 52° and 107 atm.; the solution was filtered and the ethanol distilled. The product yielded on distillation fractions (1,2,3) of (±)-4-phenylpentan-2-ol (i); fraction (2) on redistillation gave fractions (4,5,6) [Found, for (5): C, 79·8; H, 9·75. Calc. for $C_{11}H_{16}O$: C, 80·45; H, 9·8%]. Nenitzescu, Gavat, and Cocora [9] (who do not discuss diastereoisomerism) report b. p. 124—125°/15 mm.

Fraction	1	2	3	4	5	6
B. p./11 mm.	118—119	119—120	120—121	118	118—119	119—120°
n_D^{25}	1·5090	1·5100	1·5100	1·5098	1·5101	1·5100
Wt. (g.)	0·8	11·6	1·5	1·0	6·0	3·9

To a solution of (±)-4-phenylpentan-2-ol [(5) and (6); 9·06 g.] in acetic acid (30 ml.), placed in an oil-bath at 80°, a suspension of powdered chromic anhydride (6·55 g.) in acetic acid (40 ml.) was added during 15 min., with stirring which was continued for a further 15 min. The solution was cooled and poured into water (100 ml.); the whole was extracted with light petroleum (b. p. 40—60°); the extract was washed with aqueous sodium hydrogen carbonate, and with water, and dried ($MgSO_4$), and the solvent distilled. The product yielded, on redistillation, (±)-4-phenylpentan-2-one (i; 2·14 g.), b. p. 116—117°/14 mm., n_D^{25} 1·5048, n_D^{15} 1·5091 (Found: C, 81·55; H, 8·45. Calc. for $C_{11}H_{14}O$: C, 81·45; H, 8·7%). The semicarbazone, recrystallised from aqueous ethanol, had m. p. 140—141° (Found: N, 18·8. Calc. for $C_{12}H_{17}N_3O$: N, 19·15%). Closely similar fractions of ketone totalled 3·78 g. Colonge and Pichat [10] record b. p. 109°/11 mm., n_D^{15} 1·5090, for the ketone, and m. p. 137° for the semicarbazone.

Hydrogenation of (±)-4-phenylpent-3-en-2-ol (15·0 g.) was repeated under conditions similar to the above (total time 7 hr. 30 min., maximum temperature and pressure 52° and 106 atm.). Fraction (5) (5·7 g.) of the resultant (±)-4-phenylpentan-2-ol (ii) had b. p. 115—116°/9 mm., n_D^{25} 1·5102. On oxidation this (5·45 g.) gave (±)-4-phenylpentan-2-one (ii) (1·4 g.) having b. p. 117—118°/15 mm., n_D^{25} 1·5047, and closely similar fractions totalling 2·17 g.

Vapour-phase Chromatography.—The conditions for chromatography of the phenylpentan-ols and -ones were: Column: 120 × 0·4 cm. Temp., 150°. Packing: 20% tritolyl phosphate on 72—100 mesh Celite 545. Carrier gas: argon, with Lovelock ionisation detector. Inlet pressure: 34 cm. Hg. Outlet pressure: atmospheric. Rate of flow: *ca.* 30 ml./min.

(±)-4-Phenylpent-3-en-2-ol, when subjected to chromatography at 150°, decomposed on the column; at 100° it was retained so long that no chromatogram was obtained.

[9] Nenitzescu, Gavat, and Cocora, *Ber.*, 1940, **73**, 233.
[10] Colonge and Pichat, *Bull. Soc. chim. France*, 1949, 177.

XUM

We thank Dr. J. N. Haresnape and Mr. D. H. Desty of the British Petroleum Research Centre, Sunbury-on-Thames, for making available to us the use of the vapour-phase chromatograph, and the Central Research Fund of the University of London and Imperial Chemical Industries Limited for aid from grants.

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LONDON, S.W.11. [*Received, September 5th*, 1960.]

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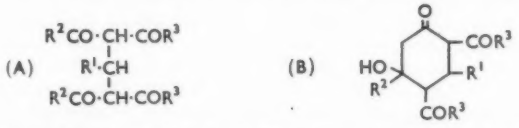
135. *The Structure of* 1,5-*Diketones.*

By I. L. FINAR.

Some aldehydes have been condensed with β-dicarbonyl compounds in molar ratio of one to two and the infrared spectra of the products have been examined. It is concluded that these bis-compounds are hydroxycyclohexanones; but this cyclic structure is only possible if there is a methyl group adjacent to a carbonyl group in the dicarbonyl compound, and in its absence the bis-compound is an acyclic 1,5-diketone. 4-Formyl-1-phenylpyrazole behaves abnormally with benzoylacetone and dibenzoylmethane, one product being 1-phenyl-3-(1-phenyl-4-pyrazolyl)prop-2-en-1-one. The reaction between some of the bis-compounds and hydrazine or phenylhydrazine has also been examined.

CONDENSATION of aliphatic or aromatic aldehydes with β-keto-esters or β-diketones, in molar ratio of one to two and in the presence of a basic catalyst, leads to bis-compounds. Various aldehydes, β-keto-esters, and β-diketones have been used (see, *e.g.*, Rabe and Elze,[1a] Horning and Field,[2] and Martin, Shamma, and Fernelius [3] for literature references). According to Knoevenagel [4,5] the general structure of these bis-compounds is (A). Rabe,[1b,6,7,8] however, believed that these compounds are hydroxycyclohexanones (B) and that eight (±)-isomers were possible; and, in the case of the benzaldehyde bis-ester (R^1 = Ph; R^2 = Me, R^3 = OEt), Rabe [6] isolated three of these (±)-forms. Further, Rabe and Elze [1a] concluded that 1,5-diketones with a methyl group attached to one carbonyl group change to cyclic alcohols under the influence of basic substances. The usual catalyst for these condensations is piperidine, and a ketone (A), which is formed first, undergoes the intramolecular aldol condensation to give (B) if allowed to remain in contact



with piperidine. According to Rabe and Elze compounds (A) form dihydropyridine derivatives (with ammonia), disodium salts, and bis-pyrazolones or -pyrazoles (with hydrazine); compounds (B) form monosodium salts and mono-pyrazolones or -pyrazoles. Knoevenagel,[5] however, believed that the change of the diketo-form (A) into its corresponding keto-enol or di-enol form, or *vice-versa*, explained the effect of piperidine on 1,5-diketones and that the existence of these forms accounted for all the chemical reactions of 1,5-diketones. Furthermore, Knoevenagel believed that the use of chemical methods

[1] Rabe and Elze, *Annalen*, 1902, **323**, (*a*) 92, (*b*) 83.
[2] Horning and Field, *J. Amer. Chem. Soc.*, 1946, **68**, 384.
[3] Martin, Shamma, and Fernelius, *J. Amer. Chem. Soc.*, 1958, **80**, 5851.
[4] Knoevenagel, *Annalen*, 1898, **303**, 223.
[5] Knoevenagel, *Ber.*, 1903, **36**, 2118.
[6] Rabe, *Annalen*, 1900, **313**, 129.
[7] Rabe and Billmann, *Annalen*, 1904, **332**, 22.
[8] Rabe, *Ber.*, 1943, **76**, 979.

XUM

to elucidate the structures of these compounds was unsatisfactory. These ideas were also held by Dieckmann and Fischer [9] who also thought that reaction with hydrazine caused the acyclic to isomerise to the ring compound.

Although the preparation of these bis-compounds requires a basic catalyst, there is at least one exception. Rabe [10] showed that formaldehyde (1 mol.) condensed directly with ethyl acetoacetate (2 mol.) to form two isomers, ethyl αα′-diacetylglutarate and ethyl 2-hydroxy-2-methyl-4-oxocyclohexane-1,5-dicarboxylate, (A) and (B) respectively ($R^1 = H$, $R^2 = Me$, $R^3 = OEt$). Also the irreversible change from acyclic to cyclic structure normally requires a basic catalyst, but the above example of cyclisation is an exception, as is also the spontaneous cyclisation of ethyl 2-acetyl-5-oxo-3,4,5-triphenylpentanoate.[11]

In the present work the known bis-esters and -β-diketones (I—VI) have been prepared (Table 1), and 4-formyl-1-phenylpyrazole [12] has been condensed, in 1 : 2 molar ratio, with

TABLE 1. *Properties of condensation products.*

No.	R^1	R^2	R^3	M. p.	Yield (%)
(IB)	Me	Me	OEt	80—81° [a]	39
(IIB)	Me	Me	Me	108 [b]	37
(IIIB)	Ph	Me	OEt	157—158 [c]	70
(IVB)	Ph	Me	Me	168—169 [d]	71
(VB)	Ph	Me	Ph	202·5—204 [e]	49
(VIA)	Ph	Ph	Ph	157—158	51
(VIIB)	1-Ph-4-$C_3H_2N_2$	Me	OEt	177—178	81
(VIIIB)	1-Ph-4-$C_3H_2N_2$	Me	Me	146—148	72
(IXB)	1-Ph-4-$C_3H_2N_2$	Me	Ph	218—219	13
(XD)	Me	Me	OEt	265—267 [g]	90
(XIF)	Me	Me	Me	195—197	54
(XIIC)	Ph	Me	OEt	192—193 [h]	57
(XIIID)	Ph	Me	OEt	278·5—280 (dec.)	70
(XIVE)	Ph	Me	Me	182—183 [j]	49
(XVF)	Ph	Me	Me	211—212 [k]	70
(XVID)	1-Ph-4-$C_3H_2N_2$	Me	OEt	267—268	63
(XVIIF)	1-Ph-4-$C_3H_2N_2$	Me	Me	206—209	57

	Found (%)				Calculated (%)		
No.	C	H	N	Formula	C	H	N
(VIIB)	64·0	6·3	7·0	$C_{22}H_{26}N_2O_6$	63·7	6·3	6·8
(VIIIB)	67·7	6·3	7·6	$C_{20}H_{22}N_2O_4$	67·8	6·2	7·9
(IXB)	74·9	5·2	5·6	$C_{30}H_{26}N_2O_4$	75·3	5·4	5·9
(XIF)	64·7	7·9	12·6	$C_{12}H_{18}N_2O_2$	64·9	8·1	12·6
(XVID)	62·55	6·1	14·4	$C_{20}H_{22}N_4O_4$	62·8	5·8	14·7
(XVIIF)	68·5	6·3	15·6	$C_{20}H_{22}N_4O_2$	68·6	6·3	16·0

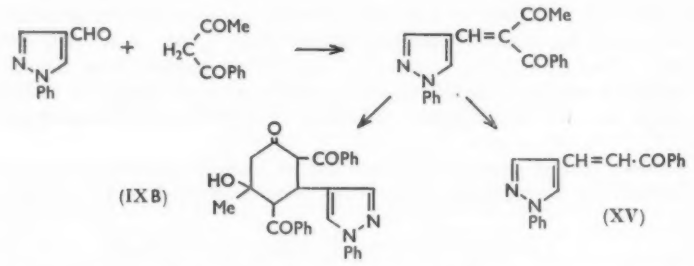
[a] Knoevenagel, *Annalen*, 1894, **281**, 104, gives m. p. 79—80°; Rabe and Billmann, *ibid.*, 1904, **332**, 26, give m. p. 80°. [b] Knoevenagel, Bialon, and Ruschhaupt, *Ber.*, 1903, **36**, 2149, give m. p. 108°. [c] Hantzsch, *Ber.*, 1885, **18**, 2583, gives m. p. 152—153°; Rabe, *Annalen*, 1900, **313**, 176, gives m. p. 149—150°. [d] Knoevenagel and Werner, *Annalen*, 1894, **281**, 81, give m. p. 166°; Schiff, *ibid.*, 1899, **309**, 206, gives m. p. 168°; Martin, Shamma, and Fernelius, *J. Amer. Chem. Soc.*, 1958, **80**, 5852, give m. p. 165—167°. [e] Knoevenagel and Erler, *Ber.*, 1903, **36**, 2131, give m. p. 195°; Martin *et al.* (ref. *d*) give m. p. 202—202·5°. [f] Dieckmann and Fischer, *Ber.*, 1911, **44**, 974, give m. p. 154—155°. [g] Rabe and Elze, *Annalen*, 1902, **323**, 100, give m. p. 256° (decomp.). [h] Rabe and Elze, *Annalen*, 1902, **323**, 103, give m. p. 168—171° (or 194°); Knoevenagel and Heeren, *Ber.*, 1903, **36**, 2124, give m. p. 193°. [i] Rabe and Elze, *Annalen*, 1902, **323**, 104, give m. p. 257° (decomp.). [j] Knoevenagel, *Annalen*, 1894, **281**, 83, gives m. p. 177°. [k] Rabe and Elze, *Annalen*, 1902, **323**, 111, give m. p. 220° (decomp.).

ethyl acetoacetate, acetylacetone, benzoylacetone, and dibenzoylmethane in the presence of piperidine. Ethyl acetoacetate gave the bis-compound (VIIB) even when the molar ratio of reactants was one to one. Acetylacetone behaved normally to give a bis-derivative (VIIIB), but with benzoylacetone the bis-(β-diketone) (IXB) was obtained together with

[9] Dieckmann and Fischer, *Ber.*, 1911, **44**, 966.
[10] Rabe, *Annalen*, 1904, **332**, 2; Rabe and Rahm, *ibid.*, 1904, **332**, 11.
[11] Rabe and Ehr, *Annalen*, 1908, **360**, 272.
[12] Finar and Lord, *J.*, 1959, 1819.

XUM

1-phenyl-3-(1-phenyl-4-pyrazolyl)prop-2-en-1-one (XV).[12] There is much evidence to show that the preparation of the bis-compounds involves an intermediate of the type $R^1{\cdot}CH{=}C(COR^2){\cdot}COR^3$, which then readily undergoes the Michael condensation with a second molecule of β-diketo-compound. Thus the formation of compounds (VIIIB)



and (IXB) is normal, but at the same time some of the intermediate unsaturated compound eliminates an acetyl group.

With dibenzoylmethane, the only product isolated was the pyrazolylpropenone (as XV). Hence in this case the Michael condensation does not appear to occur, and a benzoyl group is eliminated from the intermediate. It is interesting in this connexion that condensation of acetylacetone with cinnamaldehyde,[13] 2-hydroxynaphthaldehyde,[14] and salicylaldehyde[15] does not proceed beyond the stage of the unsaturated compound, but no mention is made of an acetyl group's being eliminated.

The infrared absorption spectra of many bis-(β-diketones) have been examined by Martin *et al.*[3] who found that all their compounds gave a wine colour with methanolic ferric chloride; they state that " in the solid state, some bis-(β-diketones) of the type $R^1{\cdot}CH[CH(COR^2){\cdot}COR^3]_2$ may exist to an appreciable extent in the keto-form." The evidence given for this is the high-intensity carbonyl absorption in the 1733—1709 cm.$^{-1}$ region and the relatively low-intensity enol-chelate absorption near 1600 cm.$^{-1}$. It is also pointed out that most of these bis-(β-diketones) have hydroxyl stretching frequencies near 3390 cm.$^{-1}$.

An interesting point about this work is that the authors apparently do not consider at all the possibility of a cyclic structure for these compounds, and make no mention of Rabe's work. In the present work the infrared absorption spectra of the bis-compounds (I—IX) show that all except (VIA) have ring structure (B). None of these gave a colour with ferric chloride. [Among the compounds examined by Martin *et al.* are (IV) and (V), and these are stated as giving a colour with ferric chloride.] A number of enolic β-diketones have also been examined and for all there was complete absence of a true alcoholic hydroxyl group absorption near 3700 cm.$^{-1}$, and in all cases a weak band near 2700 cm.$^{-1}$ which we attribute to the chelated hydroxyl group in agreement with Rasmussen, Tunnicliff, and Brattain.[16] The compounds examined (in Nujol mull) were benzoylacetone, *m*- and *p*-nitrobenzoylacetone, *p*-methoxybenzoylacetone, dibenzoylmethane, *m*-nitrodibenzoylmethane, 3-benzoylacetyl-1,5-diphenylpyrazole,[17] octane-2,4,5,7-tetraone,[17] and 1,6-diphenylhexane-1,3,4,6-tetraone.[17] All these compounds give a colour with ferric chloride and consequently are at least partly enolic.

All the spectra of (I—IX), except that of (VIA), fall into the same general pattern (Table 2) showing a strong band between 3500 and 3324 cm.$^{-1}$. This indicates the presence

[13] Knoevenagel and Herz, *Ber.*, 1904, **37**, 4483.
[14] Knoevenagel and Schröter, *Ber.*, 1904, **37**, 4489.
[15] Knoevenagel and Arnot, *Ber.*, 1904, **37**, 4499.
[16] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.
[17] Finar, *J.*, 1955, 1205.

XUM

of a " true " hydroxyl group and not an enolic chelated hydroxyl group. For compounds (I—IV) and (VII), the hydroxyl stretching frequencies are between 3550 and 3450 cm.$^{-1}$, and this could be due to intramolecularly bonded hydroxyl group or singly linked alcohol dimer.[18a] It is suggested here that the former holds in this case since diacetone alcohol [18b]

TABLE 2. *Infrared spectra of the condensation products.*

No.	O–H stretch (cm.$^{-1}$)	tert. OH C–O stretch O–H bend (cm.$^{-1}$)	C=O stretch (cm.$^{-1}$)	C=C stretch (cm.$^{-1}$)	CH stretch of CH_2 (cm.$^{-1}$)
IB	3487s	1124m, 1393sh	1745s, 1712s	—	2926m*, 2872sh
IIB	3502s	1124m	1724s, 1706s 1695s	—	2920w, 2871w
IIIB	3484m	1124sh	1748s, 1714s	1600sh, 1500sh	2926m*, 2865w
IVB	3636s	1117w, 1389m	1724s, 1704s	1610w, 1502w	2921m, 2847sh
VB	3354s	1127w, 1395sh	1709s, 1692s	1605m, 1502s	2920m, 2847sh
VIA	—	1117w	1695s, 1681s	1600m, 1502sh	—
VIIB	3448s	1124sh, 1389s	1745s, 1724s 1709s	1605s, 1508s	2920sh,* 2872sh
VIIIB	3324s	1124sh, 1404w	1724s, 1709sh 1695s	1603w, 1508w	2921m, 2847sh
IXB	3406s	1124sh, 1399sh	1709s, 1678s	1608m, 1511w	2920m, 2877sh
a	3448m	1124m, 1393m			2926m, 2855sh
b	3600m, 3490w				2920s, 2849s

1-Methylcyclohexanol: (*a*) liquid capillary film, (*b*) 0·115M-solution in CCl_4; compensated 0·5 mm. cell.

* These compounds contain a CO_2Et group and consequently a CH_2 group.

absorbs at 3484 cm.$^{-1}$ and the carbonyl absorption [18c] occurs at 1712 cm.$^{-1}$. The influence of hydrogen bonds on certain carbonyl groups [18c] is not greater than 10 cm.$^{-1}$, and it will be seen that the carbonyl frequencies of (I—IV) and (VII) are those expected (see below). On the other hand, the hydroxyl frequencies of compounds (V), (VIII), and (IX) are in the 3400—3200 cm.$^{-1}$ region, but much closer to the former, and hence these compounds also contain some polybonded alcohol.[18a]

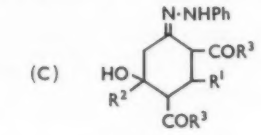
All the compounds show a peak at or near 1124 cm.$^{-1}$ and this is consistent with the C–O stretching frequency of a tertiary alcohol (near 1140 cm.$^{-1}$).[18d] Since this band could also arise from a CH in-plane deformation of a monosubstituted benzene ring (1175—1125 cm.$^{-1}$),[18e] the presence of a tertiary hydroxyl group is rendered uncertain when a monosubstituted benzene ring is known to be present. It is significant, however, that in the compounds in Table 2 this band is also present for compounds (I) and (II) in which there are no benzene rings. Further, the presence in most cases of a second band near 1393 cm.$^{-1}$ supports the argument that these compounds are tertiary alcohols, since the O–H bending frequency lies in the 1400—1300 cm.$^{-1}$ region [18f] (no similar band occurs in spectra of aromatic compounds).

All the carbonyl bands are strong and sharp and occur in the 1748—1678 region. In the spectra of the β-diketones examined above, strong broad peaks occur in the 1640—1540 cm.$^{-1}$ region, in keeping with the observation by Rasmussen *et al.*[16]. Thus the bis-compounds are ketonic compounds and not chelated ketones. Further, enolic β-diketones usually absorb near 1600 cm.$^{-1}$, but since this band (and the one near 1500 cm.$^{-1}$) is characteristic of the aromatic ring,[16g] it may sometimes be difficult to differentiate between the 1600 cm.$^{-1}$ band for C=C in-plane vibration and the 1600 cm.$^{-1}$ band for a chelated carbonyl group.[16h] Table 2 shows the 1600 and 1500 cm.$^{-1}$ bands, and it is significant that both of these are absent from the spectra of ketones (I) and (II), neither of which contains an aromatic (or heterocyclic) nucleus. It is therefore concluded that no enol form is present (cf. the fact that none gave the ferric chloride reaction). Finally, all the

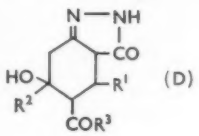
[18] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, 1958, 2nd edn., pp. (*a*) 102, (*b*) 99, (*c*) 136, (*d*) 109, (*e*) 82, (*f*) 110, (*g*) 69, (*h*) 74, (*i*) 15.

products except (VIA) showed two bands due to C–H stretching vibrations of the CH_2 group (2926 and 2853 $\pm$10 cm.$^{-1}$).[16i] In all the compounds other than those containing ethoxycarbonyl groups, there cannot be a CH_2 group present in form (A), but this group is present in the cyclic compounds (B). The OH and CH_2 bands of 1-methylcyclohexanol have been given in Table 2 (*a* and *b*) for comparison. Compound (VIA), in which there is no methyl group adjacent to a carbonyl group and which consequently cannot cyclise, shows no OH or CH_2 bands, but does show free CO bands.

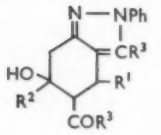
Some of the bis-compounds were treated with an excess of phenylhydrazine or hydrazine. In all cases only one mol. of reagent was used, to give products (X—XVII). The bis-esters gave either the phenylhydrazone (C) or the hexahydroindazolone (D), and the bis-



(C)

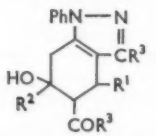


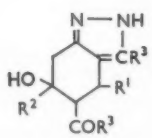
(D)



(E)

or





(F)

diketones gave the tetrahydroindazole (E) or (F). The infrared spectra of these compounds were complicated, but all showed the presence of a tertiary hydroxyl group and a methylene group.

From the foregoing discussion, it is concluded that all the bis-compounds in Table 1, except (VIA), are hydroxycyclohexanones, but it appears that before the acyclic or cyclic structure can be assigned to this type of compound, the properties of each one must be studied, and a satisfactory method is by infrared spectroscopy.

Experimental

Preparation of Hydroxycyclohexanones (I—VIII).—Ethyl acetoacetate (0·1 mole) or the β-diketone (0·1 mole) and the aldehyde (0·05 mole) were dissolved in ethanol (25—100 c.c.), with warming if necessary; piperidine (0·5—1·0 c.c.) was added and the mixture set aside at room temperature (III, IV, V, VII, and VIII), at 0° to −5° (I and II), or at 50—60° (VI), for 1—3 days. The precipitate was collected, washed with ethanol, and recrystallised from ethanol (see Table 1). None of the hydroxycyclohexanones (I—IX), in ethanol, gave a colour with neutral ferric chloride solution.

Preparation of Hydroxycyclohexanone (IX).—4-Formyl-1-phenylpyrazole [12] (3·44 g., 0·02 mole) and benzoylacetone (6·48 g., 0·04 mole) were dissolved in hot ethanol (50 c.c.), piperidine (6 drops) was added, and the mixture left for 2 days. The yellow precipitate (4·5 g.) was collected, washed with ethanol, and then digested with cold chloroform (40 c.c.). The undissolved material was recrystallised three times from 1 : 2 chloroform–light petroleum, to give 2,4-*dibenzoyl*-5-*hydroxy*-5-*methyl*-4-(1-*phenyl*-4-*pyrazolyl*)*cyclohexan*-1-*one* (IX) (1·2 g.; see Table 1).

The chloroform filtrate (from the cold digestion) was evaporated to dryness and the residue recrystallised several times from ethanol, to give yellow needles, m. p. 181°, which were shown to be 1-phenyl-3-(1-phenyl-4-pyrazolyl)prop-2-en-1-one [12] by a mixed m. p. determination with an authentic specimen, and by conversion into 1,3-diphenyl-5-(1-phenyl-4-pyrazolyl)-pyrazoline,[12] m. p. 192°.

Reaction between 4-*Formyl*-1-*phenylpyrazole and Dibenzoylmethane.*—4-Formyl-1-phenyl-pyrazole (3·44 g., 0·02 mole), dibenzoylmethane (8·96 g., 0·04 mole), ethanol (50 c.c.), and piperidine (0·5 c.c.) were heated at 40—50° for 2 days, and then left for 1 day at room temperature. The precipitate was collected, washed with ethanol, and recrystallised from ethanol,

XUM

to give 1-phenyl-3-(1-phenyl-4-pyrazolyl)prop-2-en-1-one [12] (2·6 g., 52%), m. p. 181°, the identity of which was established as described above.

Reaction between Hydroxycyclohexanones and Hydrazine or Phenylhydrazine.—The hydroxycyclohexanone (0·01 mole) and hydrazine hydrate (0·02 mole) or phenylhydrazine (0·02 mole) in ethanol (30 c.c.) were heated on the steam-bath for 0·5 hr., then set aside, and the precipitate was collected and recrystallised from ethanol; compounds (XIIC) and (XIVE) were recrystallised from benzene, and (XVID) from aqueous acetic acid (see Table 1).

Infrared Absorption Spectra.—Spectra were obtained with a Perkin–Elmer model 137 fitted with sodium chloride optics or with a Grubb–Parsons model S3A fitted with lithium fluoride optics. They were taken for mulls (Nujol or Fluorolube), except 1-methylcyclohexanol (see Table 2).

I thank Mr. E. Mooney for the spectroscopic data.

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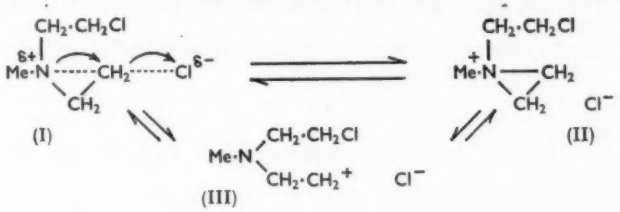
136. *The Reaction between* N-*Methyldi-*(2-*chloroethyl*)*amine and Thiosulphate.*

By E. BOYLAND and R. NERY.

N-Methyldi-(2-chloroethyl)amine reacts with an excess of thiosulphate in aqueous solution at physiological pH to yield the "Bunte" salt [$MeN(CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_3Na)_2$] which is converted into tetrahydro-5-methyl-1,2,5-dithiazepine and a polymeric disulphide in strongly alkaline media. Equimolar solutions of *N*-methyldi-(2-chloroethyl)amine and thiosulphate in water or 50% aqueous ethanol at pH 8 give perhydro-6-methyl-1,2,3,6-oxadithiazocine 2,2-dioxide in yields which appear to depend on the solubility of the product and on the dielectric constant of the reaction medium.

THE rate of the unimolecular ionisation of *N*-methyldi-(2-chloroethyl)amine hydrochloride in aqueous sodium hydrogen carbonate is much greater than that of ethyl chloride in the same medium owing to the accelerating influence of the tertiary nitrogen atom. The formation of the 1,2′-chloroethyl-1-methylaziridinium ion (II) has been demonstrated from kinetic measurements by Hanby, Hartley, Powell, and Rydon.[1] Golumbic, Fruton, and Bergmann [2] showed that the reaction rapidly produced chloride ion without an equivalent



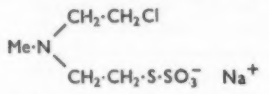
amount of hydrogen ion, and they isolated the picrylsulphonate salt corresponding to compound (II). Bartlett, Ross, and Swain [3] showed by kinetic measurements that reaction of the compound (II) with strong nucleophilic reagents ($S_2O_3^{2-}$, OH^-, Et_3N) is of first order with respect to the original tertiary base. Attack on the aziridinium ion (II) by a nucleophilic reagent weaker than the parent amine, *e.g.*, water, proceeds at a rate comparable with that of the initial ionisation; competitive attack by unchanged amine becomes evident and the kinetic course does not approximate to simple order. It is thus

[1] Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519.
[2] Columbic, Fruton, and Bergman, *J. Org. Chem.*, 1946, **11**, 518.
[3] Bartlett, Ross, and Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2971.

XUM

evident that reaction of the tertiary base with thiosulphate in aqueous sodium hydrogen carbonate is an apparent S_N1 reaction, but that attack by weaker nucleophilic reagents may involve a bimolecular process. It is thus likely, by analogy with " mustard gas," that reaction of the tertiary base with biological materials (cf. the low competition factors [4] of phosphate, carboxylate, heterocyclic tertiary nitrogen, and amino-groups at physiological pH) proceeds largely by an S_N2 mechanism. The rate of nucleophilic substitution in acidic media is considerably reduced, since protonation reduces the acceleration by the tertiary nitrogen to a minimum.

Reaction of *N*-methyldi-(2-chloroethyl)amine with one equivalent of aqueous thiosulphate gives the sodium *S*-alkyl thiosulphate (IV). Here the $CH_2{\cdot}S{\cdot}SO_3^-$ group increases the rate of the ionisation of the second 2-chloroethyl group by increasing the nucleophilic character of the tertiary nitrogen, but at the same time hinders the approach of a new nucleophilic reagent (*e.g.*, a second $S_2O_3^{2-}$ ion) by exerting an electrostatic shielding effect on, and also by direct reaction with, the seat of substitution. Direct interaction between the two reactive centres of the dipolar ion (V), or replacement of chlorine by $\cdot S{\cdot}SO_3^-$ in compound (IV), would involve transition states typical of intramolecular S_N2 reactions having lower electrostatic potentials than the reactants; one characteristic of such reactions is that the rate increases if the dielectric constant of the solvents is decreased.[5] Thus, an equimolar aqueous solution of *N*-methyldi-(2-chloroethyl)amine and sodium thiosulphate at pH 8 yielded small amounts of perhydro-6-methyl-1,2,3,6-oxadithia-azocine 2,2-dioxide (VI), but in 50% aqueous ethanol an almost quantitative yield of this base was obtained. This may appear surprising in view of the low competition factor (see below) of a negatively charged oxygen anion for a 2-chloroethyl group; precipitation of the product from solution



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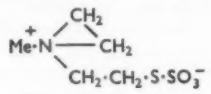
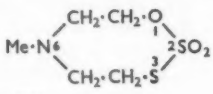


(V)

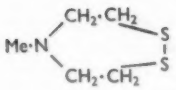


(VI)

probably accounts for the high yield. The following observations indicate that the structure assigned to compound (VI) is preferable to the alternative structures (V) and (VII) having the same empirical formula: (*a*) the substance is insoluble in cold water and in dilute alkali; (*b*) a saturated aqueous solution at 60° does not consume thiosulphate; and (*c*) high dilution has no appreciable effect on the yield. Facts (*a*) and (*b*) are incompatible with the ionic structure (V), and fact (*c*) with the polymeric structure (VII).

$$-CH_2{\cdot}CH_2-\left[NMe{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_2{\cdot}O{\cdot}CH_2{\cdot}CH_2\right]_n-NMe{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_2{\cdot}O-$$

(VII)



(VIII)

$$-CH_2{\cdot}CH_2-\left[NMe{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH_2\right]_n-NMe{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}S-$$

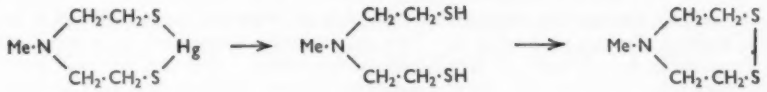
(IX)

In view of the low competition factor [4] of a negatively charged oxygen anion (SO_4^{2-}, $F = 4{\cdot}9$) compared with that of negatively charged sulphur in the thiosulphate anion ($F = 2{\cdot}7 \times 10^4$) for " mustard gas," it is unlikely that the reaction of di-(2-chloroethyl-amines with excess of aqueous thiosulphate is affected appreciably by competition involving the negatively charged oxygen of the thiosulphate ion. It is, however, significant that rather less than exactly two moles of thiosulphate are consumed per mole of tertiary base in 2 : 1 acetone–water solutions.[3]

[4] Ogston, *Trans. Faraday Soc.*, 1948, **44**, 45.
[5] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 608.

XUM

The primary substitution products of alkyl halides and thiosulphate, the so-called " Bunte " salts, have been shown [6] to undergo intermolecular reaction in alkaline media to yield the corresponding disulphides. It is now reported that the " Bunte " salt from *N*-methyldi-(2-chloroethyl)amine, *i.e.*, $Me{\cdot}N(CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_3^-Na^+)_2$, reacts further in strongly alkaline solution to yield a mixture of disulphides (VIII) and (IX), resulting from intramolecular and intermolecular interaction, respectively. A product analogous to (XII) has been prepared by reaction of di-(2-chloroethyl)amine with sodium disulphide.[7] The size of the polymer (IX) apparently varies with the concentration, basicity, and time and temperature of heating since the product varies from a viscous gum to a rubbery material.



(X) (XI) (XII)

These polymers are insoluble in water and alkali but dissolve in strong mineral acids. They are reduced by zinc and hydrochloric acid to products, probably thiols, that are converted to varying extents in alkaline solutions into tetrahydro-5-methyl-1,2,5-dithiazepine (VIII), a yellow oil characterised as its crystalline picrate and *N*-methiodide. It is reduced by zinc and acetic acid to a dithiol that has been isolated as its mercury derivative, probably (X). An aqueous suspension of compound (X), on treatment with hydrogen sulphide, yields the theoretical amount of mercuric sulphide; the liberated dithiol (XI) reverts to the cyclic disulphide (VIII) in alkaline solution.

Alkylating agents, including " nitrogen mustard," are known to react rapidly with thiosulphate to give non-toxic derivatives.[8] The present work developed out of an attempt to use the reaction of " nitrogen mustards " with sodium thiosulphate for the estimation of the former in biological fluids, but this was not pursued because the reaction with 4-4′-nitrobenzylpyridine [9] proved a more convenient method.

Experimental

Perhydro-6-methyl-1,2,3,6-oxadithiazocine 2,2-Dioxide (VI).—(a) *In 50% aqueous ethanol.* A solution of *N*-methyldi-(2-chloroethyl)amine hydrochloride (5·7 g., 0·03 mole) in ethanol (25 ml.) was added to one of sodium thiosulphate heptahydrate (7·5 g., 0·03 mole) in water (25 ml.) containing sodium hydrogen carbonate (5·0 g.). The mixture was kept at room temperature for 1 hr., then for 60 hr. at 0°. The precipitate (A) (3·0 g.), m. p. 216—220° (decomp.), was filtered off and the bulk of the alcohol was removed from the filtrate by azeotropic distillation. The residual liquid, on cooling, yielded a solid (2·5 g.), m. p. and mixed m. p. with solid (A), 216—220° (decomp.). The two solids were combined and recrystallised twice from water, to yield colourless prisms of the basic *sulphone* (VI) (5·0 g., 81%), m. p. 224° (decomp.) (Found: C 29·1; H, 5·6; N, 6·8; S, 31·2; H_2O, 4·2. $C_5H_{11}NO_3S_2,\frac{1}{2}H_2O$ requires C, 29·1; H, 5·9; N, 6·8; S, 31·1; H_2O, 4·3%).

(b) *In aqueous solution.* *N*-Methyl di-(2-chloroethyl)amine hydrochloride (5·7 g., 0·03 mole) was added to one of sodium thiosulphate heptahydrate (7·5 g., 0·03 mole) in water (50 ml.) containing sodium hydrogen carbonate (5 g.). The free tertiary base separated as an oil. The mixture was shaken rapidly at room temperature for 3 hr., giving a homogeneous solution, then kept at 0° overnight, and the precipitated solid (0·85 g.) was isolated and identified as the sulphone (VI), m. p. and mixed m. p. 224° (decomp.).

(c) *In dilute 50% aqueous ethanol.* *N*-Methyldi-(2-chloroethyl)amine hydrochloride (2·8 g.,

[6] Stutz and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 1242; Schoberl and Bauer, *Angew. Chem.*, 1957, **69**, 478.
[7] Günther and Mautner, *J. Amer. Chem. Soc.*, 1960, **82**, 2762.
[8] Cf. Callaway and Pearce, *Brit. J. Pharmacol.*, 1958, **13**, 395.
[9] Epstein, Rosenthal, and Ess, *Analyt. Chem.*, 1955, **27**, 1435.

XUM

0·015 mole) was added to a solution of sodium thiosulphate hydrate (3·7 g., 0·015 mole) in 50% aqueous ethanol (500 ml.) containing sodium hydrogen carbonate (2·5 g.), and the whole was kept at room temperature for 1 hr. and at 0° for 16 hr. The solution was concentrated *in vacuo* to about 20 ml. and, on cooling, deposited a solid (2·6 g.) which after two crystallisations from water gave compound (VI) (2·4 g.), m. p. and mixed m. p. 224° (decomp.).

Tetrahydro-5-methyl-1,2,5-dithiazepine (VIII).—(a) *From the "Bunte" salt.* *N*-Methyldi-(2-chloroethyl)amine hydrochloride (1·9 g.) was shaken with a solution of sodium thiosulphate heptahydrate (5·0 g.) in water (50 ml.) containing sodium hydrogen carbonate (2 g.) and at room temperature for 8 hr. A small precipitate was formed. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with boiling absolute ethanol (2 × 30 ml.) and the combined ethanol extracts were reduced to 5 ml. on the steam-bath. On cooling, the solution deposited a solid (0·82 g.) which failed to melt below 350° and contained sodium, nitrogen, and sulphur. This was heated in 4N-potassium hydroxide (10 ml.) on the steam-bath for 40 min., a brown colour developing. The mixture was cooled and extracted with ether (3 × 15 ml.), and the combined extracts were washed with water (2 × 10 ml.), dried (Na_2SO_4), and evaporated at 40°. The residual brown liquid, on treatment with saturated aqueous picric acid (15 ml.), gave *tetrahydro-5-methyl-1,2,5-dithiazepinium picrate* which crystallised from ethanol as yellow needles (0·02 g.), m. p. 209° (Found: C, 34·8; H, 3·7. $C_{11}H_{14}N_4O_7S_2$ requires C, 34·9; H, 3·7%).

(b) *Directly from* N-*methyldi-(2-chloroethylamine hydrochloride and excess of thiosulphate.* A solution of *N*-methyldi-(2-chloroethyl)amine hydrochloride (6·0 g., 0·0314 mole) in ethanol (10 ml.) was treated with one of sodium thiosulphate hydrate (19·8 g., 0·08 mole) in water (40 ml.), and the mixture adjusted to pH 8 with 2N-potassium hydroxide and heated with stirring at 80° for 1 hr. Potassium hydroxide (10 g.) in water (30 ml.) was then added dropwise during 20 min. to the stirred mixture at 80°. After a further 30 min., during which the mixture became brown and an insoluble viscous polymer (2·4 g.) (IX) was formed, the mixture was cooled and extracted with ether (3 × 40 ml.). The combined ether extracts were washed with water (2 × 10 ml.) and dried (Na_2SO_4), and the solvent was removed through a 20″ fractionating column. The residual brown liquid (1·2 g.) gave the above picrate, m. p. and mixed m. p. 209°. A solution of the liquid (0·3 g.) in absolute ethanol (2 ml.) gave, on treatment with methyl iodide (1 ml.), *tetrahydro-5,5-dimethyl-1,2,5-dithiazepinium iodide*, rhombs (from methanol), m. p. 212° (decomp.) (Found: C, 25·1; H, 5·0; N, 4·8; S, 22·3; I, 43·6. $C_6H_{14}INS_2$ requires C, 24·9; H, 4·8; N, 4·8; S, 22·0; I, 43·6%).

A similar reaction but with 100 ml. of ethanol and 400 ml. of water gave 1·49 g. of the polymer and 1·82 g. of the methiodide.

The compound (VI) did not react with thiosulphate at 60° during 3 hr.

(c) *From* N-*methyldi-(2-chloroethyl)amine and sodium disulphide.* A mixture of sodium sulphide (9·6 g.) and sulphur (1·3 g.) was heated to form a clear red melt which, after cooling, was treated with a solution of sodium carbonate (6 g.) in ice-water (200 ml.). Methyldi-(2-chloroethyl)amine hydrochloride (6 g.) was added and the resulting pale green suspension containing droplets of the free base was shaken at room temperature for 4 hr. and kept at 0° overnight. A solution of potassium cyanide (0·1 g.) in 6N-sodium hydroxide (20 ml.) was added and the resulting mixture heated at 100° for 1 hr., cooled, and extracted with ether (4 × 50 ml.). The ether extracts were combined, washed with water (2 × 30 ml.), dried (Na_2SO_4), and evaporated *in vacuo* to yield a residual brown oil (1·2 g.). A methanolic solution of this oil, on treatment with methyl iodide, gave the above methiodide, m. p. and mixed m. p. 210—212° (decomp.).

Mercury Derivative (X) *of* N-*Methyldi-(2-mercaptoethyl)amine.*—A solution of the disulphide (VIII) (0·45 g.) in 50% acetic acid (15 ml.) was shaken with zinc powder (0·5 g.) at 65—70° for 1 hr., then cooled and filtered, and the filtrate was adjusted to pH 6 with 2N-potassium hydroxide. On addition of 4% mercuric acetate (1 ml.), the mercury derivative (X) was precipitated as colourless rhombs (Found: Hg, 56·5. $C_5H_{11}HgNS_2$ requires Hg, 57·4%).

Conversion of the Polymer (IX) *into Tetrahydro-5-methyl-1,2,5-dithiazepine* (VII).—A solution of the polymer (1·0 g.) in 2N-hydrochloric acid (10 ml.) was heated with zinc powder at 60° for 90 min., then cooled and filtered. The filtrate was treated with 4N-potassium hydroxide (6 ml.), heated on the steam-bath for 15 min., cooled, and extracted with ether (2 × 10 ml.). The combined ether extracts were washed, dried (Na_2SO_4), treated with methyl iodide (0·5 ml.), and stored overnight at 0°. Tetrahydro-5,5-dimethyl-1,2,5-dithiazepinium iodide, m. p. and mixed m. p. 210—213 (decomp.), was obtained.

XUM

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137. *The Kinetics and Mechanism of Carbonyl–Methylene Condensation Reactions. Part XI.* Stereochemistry of the Products.*

By JACOB ZABICKY.

A series of condensates of the form $Z{\cdot}C_6H_4{\cdot}CH{:}CXY$ was synthesised where the groups X, Y, Z were suitably varied. Infrared spectra indicate that the aryl group and the smaller of the groups X, Y are *cis* to one other.

IN Parts VI—IX [1] of this series the mechanism of the condensation (1) was discussed when Ar was a substituted phenyl group, and X, Y were CN, CO_2Et, or $CO{\cdot}NH_2$. Reaction (1)

$$Ar{\cdot}CHO + CH_2XY \rightleftharpoons Ar{\cdot}CH{:}CXY + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

was carried out in water or 95% ethanol, usually without a catalyst. In this paper we discuss the configuration of the products prepared by standard procedures; the results are used in the following paper to throw light on the mechanism of the reaction.

It was shown by Baker and Howes [2] that ethyl α-cyano-β-*o*-hydroxyphenylacrylate obtained by condensation of salicylaldehyde and ethyl cyanoacetate has the *trans*-configuration (*o*-hydroxyphenyl and ethoxycarbonyl *trans* to one other). They also showed that the *cis*-isomer changes spontaneously on melting into the more stable *trans*-isomer. In this paper we show that the *trans*-form is obtained by condensing ethyl cyanoacetate or cyanoacetamide with a substituted benzaldehyde. The direct demonstration used by Baker and Howes—cyclisation of the acrylic acid to the coumarin—could not be applied to our case, and it was thought feasible to prove the configuration by infrared spectrophotometry, by correlating characteristic absorption bands of three groups.

Table 1 gives frequencies of absorption bands for characteristic stretching modes of the carbon–carbon double bond, the carbon–oxygen double bond, and the carbon–nitrogen triple bond, of a series of products obtained by reaction (1).

(A) *Carbon–Carbon Double-bond Stretching Band.*—Compounds $Z{\cdot}C_6H_4{\cdot}CH{:}C(CN)Y$, with a wide variety of Z and Y groups (I—XXIV), have bands in the same range, *i.e.*, 1582—1629 cm.$^{-1}$. Derivatives of ethyl malonate and malonamide (XXV—XXXVII) have this absorption band in a higher frequency range, *i.e.*, 1637—1681 cm.$^{-1}$ (except XXVI and XXVII). Derivatives of malonamide have the highest frequencies (*ca.* 1667—1681 cm.$^{-1}$), although the exact position of this band is not clearly defined owing to overlapping of the C=O absorption band.

(B) *Carbon–Oxygen Double-bond Absorption Bands.*—In dealing with these bands we divide the compounds IX—XXXVII into two separate groups: the esters (IX—XVI, XXV—XXXII) and the amides (XVII—XXIV, XXXIII—XXXVII).

C=O stretching bands of compounds IX—XVI are at relatively lower frequencies

* Part X, *Bull. Res. Council Israel*, 1959, **8**, *A*, 179.

[1] Parts VI—IX, *J.*, 1960, 2020—2044.
[2] Baker and Howes, *J.*, 1953, 119.

(1707—1734 cm.$^{-1}$) than those of compounds XXV—XXXII (1724—1747 cm.$^{-1}$); *i.e.*, derivatives of ethyl cyanoacetate have the absorption at lower frequencies than derivatives of ethyl malonate. This trend is reversed for the set of amides studied: derivatives of

TABLE 1. *Characteristic absorption bands* [1] [ν (*cm.*$^{-1}$)] *and physical properties of condensates* Z·C$_6$H$_4$·CH:CXY.

No.	Z	X	Y	C=C	C=O	C≡N	Synthetic method [2]	M. p.
I [3]	H	CN	CN	1603	—	2255	1	85·5—86°
II [3]	*p*-MeO	,,	,,	1620	—	2255	1	116—117
III [4]	*p*-Me$_2$N	,,	,,	1629	—	2247	1	183—184
IV [5]	*p*-Me	,,	,,	1594	—	2247	1	128—130
V [3]	*p*-Cl	,,	,,	1596	—	2255	1	160
VI [6]	*p*-Br	,,	,,	1593	—	2255	1	163
VII [7]	*m*-NO$_2$	,,	,,	1610	—	2260	1	107·5—108
VIII [8]	*p*-NO$_2$	,,	,,	1596	—	2260	1	159·5—160
IX [9]	H	,,	CO$_2$Et	1582	1732	2247	2	49·5
X [10]	*p*-MeO	,,	,,	1593	1724	2247	2	83
XI [11]	*p*-Me$_2$N	,,	,,	1620	1707	2234	2	128
XII [12]	*p*-Me	,,	,,	1607	1732	2242	2	92
XIII [13]	*p*-Cl	,,	,,	1603 1629	1734	2255	2	92
XIV [6]	*p*-Br	,,	,,	1594 1627	1734	2255	2	97·5
XV [14]	*m*-NO$_2$	,,	,,	1618	1724	2255	1	135
XVI [15]	*p*-NO$_2$	,,	,,	1607 1627	1733	2255	1	170
XVII [16]	H	,,	CO·NH$_2$	1603	1699	2247	3	123·5
XVIII [17]	*p*-MeO	,,	,,	1593	1701	2242	3	213
XIX [6]	*p*-Me$_2$N	,,	,,	1623	1689	2234	1	199—200
XX [6]	*p*-Me	,,	,,	1600	1689	2237	3	159—161
XXI [3]	*p*-Cl	,,	,,	1594	1707	2234	1	208—209
XXII [6]	*p*-Br	,,	,,	1588 1603	1695	2234	1	220—221
XXIII [6]	*m*-NO$_2$	,,	,,	1620	1701	2255	3	161—163
XXIV [3]	*p*-NO$_2$	,,	,,	1607	1701	2255	1	236—237
XXV [18]	H	CO$_2$Et	CO$_2$Et	1654	1747	—	4	(b. p. 164—165°/6 mm.)
XXVI [19]	*p*-MeO	,,	,,	1620	1740	—	4	(b. p. 180°/11 mm.)
XXVII [20]	*p*-Me$_2$N	,,	,,	1596	1737	—	2	110—111
XXVIII [21]	*p*-Me	,,	,,	1642	1737	—	4	(b. p. 240°/60 mm.)
XXIX [19]	*p*-Cl	,,	,,	1645	1740	—	4	(b. p. 171—173°/1 mm.)
XXX [6]	*p*-Br	,,	,,	1640	1737	—	4	(b. p. 176°/2 mm.)
XXXI [22]	*m*-NO$_2$	,,	,,	1637	1724	—	4	74·5
XXXII [23]	*p*-NO$_2$	,,	,,	1620 1645	1740	—	2	92—92·5
XXXIII [24]	H	CO·NH$_2$	CO·NH$_2$	*ca.* 1667	*ca.* 1667	—	3	190—191
XXXIV [6]	*p*-MeO	,,	,,	*ca.* 1678	*ca.* 1678	—	3	206
XXXV [6]	*p*-Br	,,	,,	*ca.* 1667	*ca.* 1667	—	3	217—219
XXXVI [6]	*m*-NO$_2$	,,	,,	*ca.* 1681	*ca.* 1681	—	5	211
XXXVII [6]	*p*-NO$_2$	,,	,,	*ca.* 1673	*ca.* 1673	—	5	211

[1] All absorptions are strong. [2] See Experimental part. [3] Part VI, *J.*, 1960, 2020. [4] Sachs and Lewin, *Ber.*, 1902, **35**, 3577. [5] Gal, Fung, and Greenberg, *Cancer Res.*, 1952, **12**, 565. [6] See Table 2. [7] Kaufmann and Jeutter, *Ber.*, 1917, **50**, 523. [8] Hertel and Hoffman, *Z. phys. Chem.*, 1941, **50**, *B*, 390. [9] Carrick, *J. prakt. Chem.*, 1892, **45**, 501. [10] Bechert, *J. prakt. Chem.*, 1894, **50**, 10. [11] Bauer and Seyforth, *Ber.*, 1930, **63**, 2691. [12] Fiquet, *Ann. Chim. Phys.*, 1893, **29**, 479. [13] von Walter and Raetze, *J. prakt. Chem.*, 1902, **65**, 284. [14] Sudborough and Lloyd, *J.*, 1898, **73**, 88. [15] Stuart, *J.*, 1883, **43**, 408. [16] Day and Thorpe, *J.*, 1917, **117**, 1465. [17] Curtis and Day, *J.*, 1923, **123**, 3131. [18] Allen and Spangler, *Org. Synth.*, Coll. Vol. 3, 1955, p. 377. [19] Ogata and Tsuchida, *J. Amer. Chem. Soc.*, 1959, **81**, 2092. [20] Wayne and Cohen, *J.*, 1925, **127**, 459. [21] Pratt and Werble, *J. Amer. Chem. Soc.*, 1950, **72**, 4638. [22] Ruhemann, *J.*, 1903, **83**, 723. [23] Stuart, *J.*, 1885, **47**, 158. [24] Henk, *Ber.*, 1895, **28**, 2256.

cyanoacetamide (XVII—XXIV) absorb at higher frequencies (1689—1707 cm.$^{-1}$) than those of malonamide (XXXIII—XXXVII, absorbing at 1667—1681 cm.$^{-1}$).

(C) *Carbon–Nitrogen Triple-bond Stretching Band.*—The frequency increases almost in

the order of increasing electronegativity of the substituent Z on the one hand, and in the order of increasing electronegativity of the substituent Y on the other hand; *i.e.*, derivatives of cyanoacetamide (XVII—XXIV) absorb at 2234—2255 cm.$^{-1}$, those of ethyl cyanoacetate (IX—XVI) absorb at 2234—2255 cm.$^{-1}$, and those of malononitrile (I—VIII) absorb at 2247—2260 cm.$^{-1}$. Some irregularity for the derivatives of cyanoacetamide being neglected, frequencies increase in the following order when the substituent Z is changed: *p*-Me_2N < *p*-Me < *p*-MeO < H < *p*-Cl < *p*-Br < *m*-NO_2 < *p*-NO_2.

Discussion.—The polarisation of the carbon–oxygen double bond in the esters studied (IX—XVI, XXV—XXXII) is increased by the conjugation of the styrene system with the carbonyl group. It may be expected that the cross-conjugation of a cyano-group with the ethoxycarbonyl group as in compounds IX—XVI will cause a hypsochromic shift in the carbonyl stretching frequencies with respect to those of XXV—XXXII, as the conjugation of the ring with the stronger cyano-group will be preferred; *e.g.*, Felton and Orr [3] found that a change from a 1,1-diethoxycarbonylethylene compound to a 1-cyano-1-ethoxycarbonylethylene compound causes a *hypsochromic* shift in the carbonyl stretching band of about 10 cm.$^{-1}$. In our case the same structural change causes a *bathochromic* shift of 20—30 cm.$^{-1}$.

A model of diethyl benzylidenemalonate shows that it is impossible for it to have a sterically unstrained planar conformation. In order to have two coplanar carbonyl groups with the carbon–carbon double bond and the phenyl group as nearly coplanar as possible, the *cis*-carbonyl group has to be brought near to the phenyl group, with the ethoxy-group projecting out in the opposite direction. This means that either the *cis*-carbonyl group is not coplanar with the remaining *trans*-cinnamic ester system, or the phenyl group is not coplanar with the remaining 1,1-diethoxycarbonylethylene system. In both cases a hypsochromic shift will result with respect to the carbonyl frequency of a completely planar system. A secondary effect is also to be expected as follows: when the carbonyl group that is *cis* to the phenyl group attains its easiest coplanar conformation (directed towards the phenyl group) it will suffer an electrostatic repulsion by the phenyl group, as the normal polarisation of the carbonyl group is $^{+}C–O^{-}$, with the negative end of the dipole near the electron-rich phenyl group.

If we change the *cis*-ethoxycarbonyl group to a cyano-group, the latter is favoured in the conjugation with the styrene system, but we have nevertheless relieved all the steric strain caused by a large group. Therefore the remaining *trans*-carbonyl group will be coplanar with the styrene system and will conjugate better with it, resulting in a bathochromic shift as is actually the case.

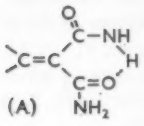
The conclusion from the above discussion is that the series of ethyl benzylidenecyanoacetates, IX—XVI, has the so-called *trans*-configuration (cyano-group *cis* to phenyl group). Further evidence for this lies in the experiments by Lohaus,[4] who obtained a mixture of *cis*- and *trans*-ethyl benzylidenecyanoacetate and showed that it was spontaneously converted into one of the isomers; it is to be expected that the *trans*-isomer is the stable one and its reported properties [4] correspond to those of IX.

The carbonyl group of the α-cyano-β-phenylacrylamides, XVII—XXIV, absorb at frequencies, 1689—1701 cm.$^{-1}$, that are lower than those of the carbonyl of the esters. This is to be expected in amides because of the hydrogen-bonding properties of the NH_2 group.[5] On the other hand, it is fair to claim that this bonding does not take place to a great extent: derivatives of malonamide, XXXIII—XXXVII, have the same kind of steric hindrance as was described for the model of diethyl benzylidenemalonate; therefore the carbonyl has to absorb at frequencies not lower than those of the derivatives of cyanoacetamide, but benzylidenemalonamides are capable of strong intramolecular

[3] Felton and Orr, *J.*, 1955, 2170.
[4] Lohaus, *Annalen*, 1934, **514**, 137.
[5] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1956, pp. 175 ff.

XUM

hydrogen bonding of the type (A). This, together with the possible intermolecular hydrogen bonding, will cause a bathochromic shift independently of the unfavourable non-planar conformation of the molecule. Strong hydrogen bonding in derivatives of cyanoacetamide would lower the frequencies of the carbonyl absorption to the same range as those of the benzylidenemalonamides. Poorly bonded carbonyl groups of cyanophenylacrylamides of *cis*-configuration are to be expected to absorb at frequencies higher than those found for XVII—XXIV owing to steric hindrance and the unfavourable cross-conjugation of the cyano-group. Therefore it may be concluded that compounds XVII—XXIV have the *trans*-configuration.


(A)

The effect found by changing the group Z on the cyano-group stretching frequencies is as expected: the cyano-group is strongly electronegative and conjugated electron-releasing groups aid its polarisation.

Experimental

Synthesis of compounds in Table 1 was accomplished by the following methods:

Method 1. Equimolecular amounts of aromatic aldehyde and active methylene compound were dissolved in the minimal amount of 95% ethanol. After the addition of a few drops of 10% potassium hydroxide solution the mixture was set aside for an hour. The precipitate was filtered off and purified by repeated recrystallisations from ethanol.

Method 2. A 0·1M-ethanolic solution of both aromatic aldehyde and active methylene compound with a few drops of piperidine was refluxed for 4—6 hr. The solvent was quickly evaporated, and the residue cooled, filtered off, and purified by repeated recrystallisations from ethanol.

Method 3. As method 1, but the reaction mixture was stored for one day at room temperature.

Method 4. A benzene solution of concentration about 3M in both aldehyde and active methylene compound with a few drops of piperidine added was refluxed with azeotropic distillation of water until it was all removed. The mixture was washed with aqueous dilute hydrochloric acid, and the benzene evaporated. If the condensation product was a liquid, it was distilled twice under low pressure; if a solid, it was recrystallised repeatedly from ethanol.

Method 5. Equimolecular amounts of aldehyde and active methylene compound were ground together in a mortar and suspended in aqueous ethanol (3 : 1) with a few drops of 10% potassium hydroxide solution and shaken for 8—10 hr. The precipitate was filtered off and purified by recrystallisations from diluted ethanol (3 : 1).

Table 2. *Data on new compounds appearing in Table* 1.

No.*	Aryl subst.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
			Benzylidenemalononitrile						
VI	*p*-Br	52	51·95	1·7	11·9	$C_{10}H_5BrN_2$	51·5	2·2	12·1
			Ethyl α-cyano-β-phenylacrylate						
XIV	*p*-Br	60	51·6	3·5	4·9	$C_{12}H_{10}BrNO_2$	51·45	3·6	5·0
			α-Cyano-β-phenylacrylamide						
XIX	*p*-NMe_2	71	66·8	5·75	20·3	$C_{12}H_{12}N_2O$	67·1	6·1	19·75
XX	*p*-Me	40	71·4	5·4	15·0	$C_{11}H_{10}N_2O$	71·6	4·1	15·3
XXII	*p*-Br	60	48·0	3·0	11·2	$C_{10}H_7BrN_2O$	47·8	2·8	11·2
XXIII	*m*-NO_2	10	55·7	3·7	19·6	$C_{10}H_7N_3O_3$	55·3	3·25	19·35
			Ethyl benzylidenemalonate						
XXX	*p*-Br	55	51·1	4·8	—	$C_{14}H_{15}BrO_4$	51·4	4·6	—
			Benzylidenemalonamide						
XXXIV	*p*-MeO	60	60·4	5·7	12·1	$C_{11}H_{12}N_2O_3$	60·0	5·5	12·7
XXV	*p*-Br	45	44·3	3·0	10·4	$C_{10}H_9BrN_2O_2$	44·1	3·4	10·5
XXXVI	*m*-NO_2	50	50·8	3·4	17·5	$C_{10}H_9N_3O_4$	51·1	3·8	17·9
XXVII	*p*-NO_2	52	51·3	3·5	17·5	$C_{10}H_9N_3O_4$	51·1	3·8	17·9

* No. XIX is orange; the others are colourless.

XUM

Data on new compounds synthesised for this investigation are given in Table 2.

Infrared spectra were determined for solids in potassium bromide pellets, and for liquids by placing a thin layer of product between two potassium bromide pellets. A Baird Associates infrared spectrophotometer, equipped with a sodium chloride prism, was used.

The author is indebted to Professor S. Patai for helpful discussions and criticism, to Mrs. H. Feilchenfeld and Mrs. E. Levi for the infrared spectra, and to Mrs. M. Goldstein and Mrs. S. Horev for the analyses.

THE HEBREW UNIVERSITY, JERUSALEM, ISRAEL. [*Received, April 25th,* 1960.]

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138. *The Kinetics and Mechanism of Carbonyl–Methylene Condensation Reactions. Part XII.*[1] *The Elimination Step of the Uncatalysed Condensation in Water.*

By JACOB ZABICKY.

The mechanism and the stereochemistry of the double-bond formation in carbonyl–methylene condensations are discussed, and a possible path for the reversal of the condensation, *i.e.*, the production of the aromatic aldehyde and the active methylene compound from the condensation product, is proposed.

IN Parts VI—IX [2] of this series it was established that condensation of active methylene compounds such as malononitrile, ethyl cyanoacetate, and cyanoacetamide in ethanol or water takes place in three main steps, namely, ionisation of the active methylene compound

$$CH_2XY \rightleftharpoons {}^-CHXY + H^+ \quad (X, Y = CN, CO_2Et, CO{\cdot}NH_2) \qquad (1)$$

nucleophilic attack of the carbanion formed on the carbonyl group of the aromatic aldehyde

$$Ar{\cdot}CH{:}O + {}^-CHXY \rightleftharpoons Ar{\cdot}CH(\bar{O}){\cdot}CHXY \qquad (2)$$

and double-bond formation that may be formally represented as

$$Ar{\cdot}CH(\bar{O}){\cdot}CHXY \rightleftharpoons Ar{\cdot}CH{:}CXY + \bar{O}H \qquad (3)$$

We now suggest for step (3) a mechanism that takes into account observations reported in preceding papers and the stereochemistry of the products, and we explain the mechanism of the reversal of the condensation, *i.e.*

$$Ar{\cdot}CH{:}CXY + H_2O \rightleftharpoons Ar{\cdot}CH{:}O + CH_2XY \qquad (4)$$

RESULTS AND DISCUSSION

A series of practically insoluble condensation products was prepared in water, in conditions similar to those of the kinetic measurements in Parts VIII and IX.[2] Precipitation of pure condensates began soon after the start of the reaction. Details of the synthesis and properties of the precipitates are given in Table 1.

The m. p.s and infrared spectra of the six precipitates in Table 1 were identical with those described in the preceding paper. It is concluded that in kinetic conditions the products have the configuration of those obtained by ordinary synthetic methods, *i.e.*, *trans* (Ia, Ib).

The alcoholate ion intermediate (II) of step (2) has two asymmetric carbon atoms when the condensation is carried out between an aromatic aldehyde and an active

[1] Part XI, preceding paper.
[2] Parts VI—IX, *J.*, 1960, 2020—2044.

XUM

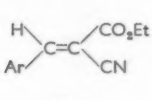
methylene compound with two different activating groups (such as cyanoacetamide and ethyl cyanoacetate). Step (2) may give rise to four diastereoisomeric intermediate ions (II), namely, two *erythro* and two *threo*. The problem is to find the elimination path

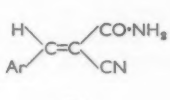
TABLE 1. *Condensation reaction of cyanoacetamide* (CA) *and ethyl cyanoacetate* (EC) *with substituted benzaldehydes* ($Z{\cdot}C_6H_4{\cdot}CHO$) *in kinetic conditions,*[2] *in water at* 40°.

Methylenic compound	Z	Time of reaction	Aldehyde reacted (%)	M. p.
CA	*p*-NO_2	2 hr.	4·8	235—236°
CA	*m*-NO_2	2·8 hr.	2·1	162
CA	*p*-Br	3·4 hr.	4·6	219
EC	*p*-NO_2	2 min.	6·2	170—171
EC	*m*-NO_2	15 min.	5·4	134·5—135
EC	*p*-Cl	4 hr.	0·2	92

Initial concentration of active methylene compound 0·01M, of *p*-bromobenzaldehyde 0·003M, and of other aldehydes 0·007M.

leading exclusively to the *trans*-condensation product from the mixture of the diastereoisomers.


(Ia)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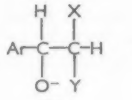
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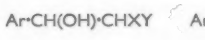
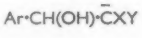
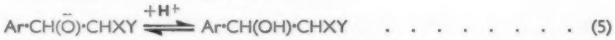
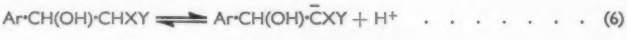

(III)

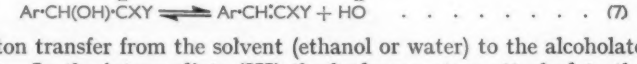

(IV)

In preceding papers of this series it was reported that reaction (4) takes place when the condensation product is dissolved in 95% ethanol or water. This hydrolysis of the double bond is catalysed by bases and retarded or even stopped by small quantities of acid. It was also reported that no intermediate was detected in the reaction mixture either during the reaction or at equilibrium, *i.e.*, any intermediate produced will always be in a very small concentration. Owing to the nature of the reaction it was not possible to draw any conclusion from the kinetic results in preceding papers on the reaction constants of steps (1), (2), and (3), and the conclusion reached in this paper are based mainly on qualitative observations.

The following mechanism is proposed for step (3):


(5)


(6)

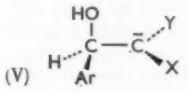

(7)

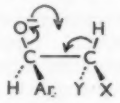
Step (5), being a proton transfer from the solvent (ethanol or water) to the alcoholate ion (II), is probably fast. In the intermediate (III) the hydrogen atom attached to the carbon atom bearing the X,Y groups is strongly activated and is expected to undergo a spontaneous ionisation (6) similar to step (1), giving rise to the carbanion (IV).

Step (7) is the elimination of a hydroxyl ion from carbanion (IV). This step is aided by the resonance stabilisation occurring on formation of the double bond. The importance of the contribution of the structures involving conjugation of the groups X,Y with the aryl group to the structure of the condensation products is apparent from their ultraviolet spectra (see Parts VI, VIII, and IX of this series).

It remains to show why this elimination path is stereospecific: the elimination path proposed above differs only in detail from an E_2 reaction in which steps (6) and (7) take place in a single step, *i.e.*, at the rate-determining step the proton is removed by a base and at the same time the anion is expelled; in our case a hydrogen ion separates in step (6) owing to the activation by the electronegative groups X, Y, and this process may take place independently of the conformation of the molecule at the time of its occurrence.

The E_2 stereochemical path is well known,[4] and diastereoisomeric compounds that undergo elimination by this mechanism are known to produce mainly one of the possible double-bond compounds, one of the diastereoisomers being used up and the other remaining almost untouched. The transition state of step (7) (as that of E_2) has to have a special


(V)


(VI)

conformation in order to permit separation of the hydroxyl group and allow the free-electron pair to form the double bond. For this to occur it is necessary that the groups X, Y take definite positions in the spatial distribution of the groups of intermediate (IV), either staggered between the hydroxyl and aryl groups, or staggered between the hydroxyl group and the hydrogen originally attached to the aromatic aldehyde, as in (V). If intermediate (IV) has to adopt conformation (V), this will be much easier when the group staggered between the phenyl and the hydroxyl groups, say X, is the smaller one of X and Y.

This process of selective elimination, similar to that taking place in E_2, will lead to the condensation product of *trans*-configuration.

This path of elimination is in agreement with the results found for the hydrolysis of the condensation product (4), *i.e.*, the hindering effect of acids on the development of this reaction and the acceleration caused by bases. As hydroxyl ions accelerate the retrograde reaction, it can be concluded, from the principle of microscopic reversibility, that they are eliminated as such in the condensation. This is reinforced by the fact that acids stop reaction (4), and it would be difficult to propose a mechanism for (4) beginning with the attack of a hydrogen ion on the condensation product. (The above arguments exclude an elimination similar to E_1 and its retrogression by electrophilic addition to the double bond.)

There is one alternative path of elimination that may be stereospecific and the retrogression of which may involve base-catalysis. This path is a four-centred elimination from intermediate (II), as described in (VI). The eclipsed conformation necessary for this elimination path gives preference to diastereoisomers (II) where the smaller of X and Y is eclipsed with the phenyl group at the time of elimination. It is hard to believe that the four-centred elimination will be able to compete successfully with the protonation (5) in solvents ethanol or water, but it remains a probable elimination path in aprotic solvents.

The retrogression of step (5), *i.e.*, the splitting of the aldol intermediate (III) into a proton and an alcoholate ion (II), is believed to be a very difficult process in water. This leads us to a new problem: as the reaction is reversible, what will be the path of the retrogression (4) if step (5) is practically irreversible? A probable way is through an internal proton transfer in intermediate (IV), from the hydroxyl group to the carbanion leading to intermediate (II). This process may take place with relative ease owing to the mobility of the free electron pair of the carbanion. The retrogression of this transfer is equivalent to the reversal of the four-centred elimination. From intermediate (II) the completion of reaction (4) follows straightforwardly by the retrogression of step (2) involving the carbon–carbon bond splitting.

The mechanism proposed above is in qualitative agreement with that proposed for the base-catalysed condensation of various substituted benzaldehydes with acetone[5] and butan-2-one.[6] Quantitative differences arise owing to the enhanced activity of the eliminated hydrogen that may be expected in intermediate (III) as compared, for instance,

[3] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, 1953.
[4] Cram, " Steric Effects in Organic Chemistry," edited by Newman, John Wiley & Sons, Inc., New York, 1956, pp. 304 ff.
[5] Noyce and Reed, *J. Amer. Chem. Soc.*, 1959, **81**, 624.
[6] Stiles, Wolf, and Hudson, *J. Amer. Chem. Soc.*, 1959, **81**, 628.

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with 4-hydroxy-4-phenylbutan-2-one.[5] The presence of a base in solution helps the hydroxy-ketone to give the corresponding alcoholate ion [5,6] in the retrogression of the condensation, but in the absence of a base the retrogression of step (5) would be very difficult.

Experimental.—Reagents were prepared as described in Parts VIII and IX.[2]

Synthesis in "kinetic conditions." Aqueous solutions of the reagents were placed in a 250 ml. volumetric flask, which was then filled with water to the mark, all being at 40°, shaken, and put in a water-bath at 40°. The precipitate obtained was filtered off, washed with water, and dried in vacuum at room temperature to constant weight (1 day).

Infrared spectra were determined in the solid state the day after the precipitates were obtained, by dispersing the compound in a potassium bromide pellet, in a Baird Associates Inc. spectrophotometer equipped with a sodium chloride prism.

The author is indebted to Professor S. Patai for helpful discussion and criticism and to Mrs. H. Feilchenfeld and Mrs. E. Levi for the infrared spectra.

THE HEBREW UNIVERSITY, JERUSALEM, ISRAEL. [*Received, April 25th,* 1960.]

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139. *The Variation of Bond Type in Cyclopentadienyl–Metal Compounds.*

By DAVID A. BROWN.

The variation of bond type in cyclopentadienyl–metal compounds with the nature of the central element is reviewed. Compounds from the elements of Groups I to IV are compared with those of the transition elements; the bonding is considered in terms of a purely ionic model, a delocalized π-complex and a localized σ-complex model. Consideration of promotion energies, group-overlap integrals, and electron-transfer energies leads to the view that the elements of Groups Ia and IIa form compounds with pronounced ionic character whereas those of Groups Ib and IIb will tend to form σ-complexes. With regard to Group IIIb and IVb it is more tentatively suggested that the thallium and indium compounds possess more covalent character than hitherto considered; for biscyclopentadienyl-lead and -tin the σ-complex is indicated. The relative success of simple molecular orbital theory in explaining the electronic structure of the transition metal–biscyclopentadienyl compounds is due, in part, to the lower promotion energies of the π-structure valency states than of the σ-structure states.

THE isolation [1] of ferrocene (biscyclopentadienyl-iron) in 1951 was followed by a rapid extension of the series $M(C_5H_5)_2$, M = metal, to many elements of the three transition series, and simple molecular-orbital-theory [2,3] has provided a reasonable explanation of bonding in such compounds. This explanation is, of course, not quantitative but the central feature seems correct; namely, that overlap of partially filled central metal *d*-orbitals with the π-orbitals of the cyclopentadienyl radicals causes considerable stabilization of the molecule $M(C_5H_5)_2$. Estimates of the energies of the respective orbitals in the isolated systems in terms of ionization potentials and promotion energies then provide a basis from which semiquantitative estimates of bond energies can be made in certain cases.[5] In addition to the transition metals, other elements form cyclopentadienyl compounds,[4] *e.g.*: triscyclopentadienylmetal compounds $M(C_5H_5)_3$, formed by lanthanides and

[1] Kealy and Pauson, *Nature*, 1951, **168**, 1039; Miller, Teboth, and Tremaine, *J.*, 1952, 632.
[2] Moffitt, *J. Amer. Chem. Soc.*, 1954, **76**, 3386; Jaffé, *J. Chem. Phys.*, 1953, **21**, 156.
[3] Dunitz and Orgel, *J. Chem. Phys.*, 1955, **23**, 954.
[4] Fischer and Fritz, "Advances in Inorganic and Radiochemistry," Academic Press New York, 1960, Vol. I, p. 55; Cotton and Wilkinson, "Progress in Inorganic Chemistry," Interscience Publ. Inc., New York, 1960, Vol. I, p. 1.
[5] Cotton and Reynolds, *J. Amer. Chem. Soc.*, 1958, **80**, 269.

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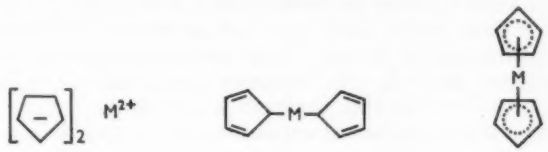
actinides (these will not be considered in this paper); and the elements of Group Ia and b, Group IIa and b, Group IIIb, and Group IVb, $M(C_5H_5)_2$ or $M(C_5H_5)$.

In general, a complex $M(C_5H_5)_2$ or $M(C_5H_5)$ may be envisaged as comprising (*a*) ionic bonding, (*b*) localised covalent bonds (σ-bonded complex), or (*c*) delocalized covalent



(*a*) (*b*) (*c*)

bonding with D_{5d} sandwich structure (π-bonded complex) (cf. Fig.); this classification has also been discussed by Fischer and Fritz.[4]

In this paper we examine, on simple theoretical grounds, the variation of bond type of the cyclopentadienyl complexes of the above groups and suggest, where possible, the most probable structure for each case. We discuss first the theoretical basis, then some of the general conclusions, and, finally, compare the theoretical results in detail with the experimental data.

Molecular orbital theory does not yield satisfactory quantitative data for, *e.g.*, bond energies and electronic levels except in very simple cases. Ideally, it is necessary, for the above complexes to set up a variational treatment and to solve the resulting secular equation:

$$|H_{ij} - S_{ij}E| = 0$$

where H_{ii}, H_{jj}, H_{ij} are the coulomb terms of the ith and jth orbital and the resonance integral between the ith and jth orbital respectively, the summation being taken over the *s*-, *p*-, and *d*-atomic orbitals of the central atom and the π-orbitals of the cyclopentadienyl radical or, in the case of a σ-complex, simply over the σ-orbital of a carbon atom of the cyclopentadienyl ring. In a satisfactory quantitative treatment it must be possible to calculate the above terms with reasonable accuracy; unfortunately, with the present development of theory, only semi-empirical methods are available. Detailed semi-empirical calculations [3] have been confined to ferrocene; these gave coulomb terms from observed ionization potentials, resonance integrals from calculated group-overlap integrals, and the promotion energy of the central atom to the correct valency state for combination with the cyclopentadienyl radicals from observed term spectra of the free atom. However, satisfactory agreement between calculated and measured bond energies on such semi-empirical models only confirms the correctness of the empirical parameters employed. Comparison between different central atoms on such a model is very difficult, indeed almost impossible, since an empirical parameter relating H_{ij} to S_{ij} may not be transferable from one element to another. In view of these uncertainties, we have restricted the argument to a consideration of valency-state promotion energies, ionization potentials, and overlap integrals as criteria for determining the most probable structure for a complex of a given element.

For an ionic compound $M^{n+}(C_5H_5^-)_n$, the energy (W) required to transfer n electrons from the central atom to the cyclopentadienyl radicals is given by the expression:

$$W = -\sum^{n} I_n + nE_{e_1} + \Delta = E_i + \Delta$$

where I_n is the nth ionization potential of the central atom, E_{e_1} is the electron affinity of the e_1-orbital of the cyclopentadienyl radical, and Δ is the difference in energy between the cation and anion, in the gas phase and the ions either in the crystal or in solution.

The values of I_n are readily available for all the elements concerned. The electron

affinity of the e_1-orbital of the cyclopentadienyl radical has been estimated by Moffitt [2] to be approximately 8 ev. It is very difficult to estimate Δ, which, in the case of the solid state, represents the lattice energy of a cyclopentadienylmetal. One would expect this quantity to be fairly small since the anion will consist of unit negative charge spread over a ring and, for a given cation, the lattice energy decreases with increasing anion size of constant charge. Thus, for the alkali-metal complexes we should expect Δ to be much less than for the alkali iodides (6—7 ev). In general we shall assume Δ to be about 2—3 ev, with the consequence that only if E_i, which we shall tabulate, is appreciably negative may we then safely conclude that ionic character is unlikely.*

For our discussion of the covalent structures (π- and σ-type), we require a knowledge of both the valency-state promotion energies and the relevant overlap integrals. The valency-state promotion energy P is the energy required to convert the free atom in its ground state to the valency state compatible with bonding interaction with the cyclopentadienyl group, for the particular model to be considered; the promotion energy varies, therefore, considerably throughout the series and we shall consider each group briefly in turn.

For the π-model, interaction in the D_{5d} group (or C_{5v} for M·C_5H_5) will be of a type previously considered.[3,5,6] The main bonding interactions will be of the form $(e_{1g}nd_{xz,yz})$ or $(e_1nd_{xz,yz})$ and $(e_{1u}np_{xy})$ or (e_1np_{xy}) where n denotes the principal quantum number of the atomic orbital of the central atom. To anticipate somewhat, we note that for Groups I—IV it is the second of the above groups of interaction which is important, in contrast to the position for the transition metals where, although there is appreciable interaction with the np-orbitals,[6] it is the former group which is dominant. The valency states of the elements of Group I (Table 1) simply involve promotion of an electron from an ns-orbital to np- or nd-orbitals and are obtained directly from the observed spectral data.[7] The elements of Group II may attain the valency state $nd^2(V_2)$ or $np^2(V_2)$ corresponding to the two groups of interaction above. The promotion energies of the latter state are available from the work of Pritchard and Skinner,[8] and spectroscopic data give no evidence for the nd^2-state below the first ionization potential; the values are again given in Table 1. In the case of elements of Group III, the most probable valency-state appears to be that suggested by Cotton and Reynolds [5] in which two electrons are paired in a s/p_z hybrid orbital directed away from the ring, leaving an empty s/p_z hybrid to overlap the filled totally symmetric π-orbital of the ring and with one electron in a $p_{x,y}$ orbital overlapping with the doubly degenerate e_1-orbital of the ring and containing three electrons. Such an electronic arrangement raises the problem of assessing the valency-state promotion energy for a configuration involving hybridized orbitals; the problem has been discussed in detail for a few special cases involving s- and p-orbitals [9] and for a wide range of hybridization of s-, p-, and d-orbitals of the first transition elements.[10] In the cases considered in this paper, however, the extent of mixing of s- and p-orbitals is not known exactly and so we have not attempted to carry out the above procedure; for example, in the case above it does not follow that equal participation of the s- and p-orbitals will occur in the two hybrids. The statement is also true of many of the valency-states of the elements when prepared for σ-bonding as discussed below. In the case of uncertain mixing of s- and p-orbitals we have therefore followed Moffitt's method [11] of estimating the approximate electron configuration s^qp^r (where q and r may be fractional) of the valency state; the

* The reliability of such conclusions is strengthened by the fact that the value of 8 ev assigned to E_{e_1} is probably too large. I thank the Referees for drawing my attention to this point.

[6] Brown, *J. Chem. Phys.*, 1958, **29**, 1086.
[7] Moore, "Atomic Energy Levels," N.B.S. Circular 467, U.S. Government Printing Office, Washington D.C., Vols. I—III.
[8] Pritchard and Skinner, *Chem. Rev.*, 1955, **55**, 745.
[9] Van Vleck, *J. Chem. Phys.*, 1934, **2**, 22.
[10] Skinner and Sumner, *J. Inorg. Nuclear Chem.*, 1957, **4**, 245.
[11] Moffitt, *Proc. Roy. Soc.*, 1950, *A*, **202**, 534.

promotion energy may then be assigned within limits, albeit rather wide limits, from Pritchard and Skinner's tables.[8] On this basis it can be shown that the above arrangement gives rise to the configuration $sp^2(V_1)$, the promotion energies being given in Table 1. It is again estimated that the state $spd(V_1)$ lies above the first ionization potential. The elements of Group IV possess the low-lying valency state $s^2p^2(V_2)$ which is directly suitable for the π-bonding through the interaction $(e_{1u}np_{xy})$. The promotion energies of the states $s^2pd(V_2)$ and $s^2d^2(V_2)$ are again estimated from spectral data and given in Table 1. The promotion energies of the first transition elements are also given in Table 1 and are taken

TABLE 1. *Promotion and ionization energies.*

Element	Electron confign.	Valency state	Promotion energy (ev)	E_i (ev)	Element	Electron confign.	Valency state	Promotion energy (ev)	E_i (ev)
Li	$2p$		1·85	+2·61	Si	$3s^23d^2$	$s^2d^2(V_2)$	>8·15	
	$3d$		3·88			$3s^23p^2$	$s^{4/3}p^{8/3}(V_2)$	<6·0	
Na	$3p$		2·10	+2·86	Ge	$4s^24p^2$	$s^2p^+p^-(V_2)$	0·31	−7·81
	$3d$		3·62			$4s^24p4d$	$s^2pd(V_2)$	~6·10	
K	$4p$		1·61	+3·66		$4s^24d^2$	$s^2d^2(V_2)$	>7·88	
	$4d$		3·40			$4s^24p^2$	$s^{4/3}p^{8/3}(V_2)$	<7·0	
Rb	$5p$		1·56	+3·82	Sn	$5s^25p^2$	$s^2p^+p^-(V_2)$	0·50	−5·97
	$5d$		3·19			$5s^25p5d$	$s^2pd(V_2)$	~5·40	
Be	$2p^2$	$p^2(V_2)$	7·30	−11·53		$5s^25d^2$	$s^2d^2(V_2)$	>7·34	
	$3d^2$	$d^2(V_2)$	>9·32			$5s^25p^2$	$s^{4/3}p^{3/8}(V_2)$	<7·0	
	$2s2p$	$sp(V_2)$	~3·36		Cu	$4p$		3·78	+0·28
Mg	$3p^2$	$p^2(V_2)$	6·87	−6·67		$4d$		6·19	
	$3d^2$	$d^2(V_2)$	>7·64		Ag	$5p$		3·66	+0·43
	$3s3p$	$sp(V_2)$	~3·12			$5d$		6·04	
Ca	$4p^2$	$p^2(V_2)$	4·84	−1·98	Zn	$4p^2$	$p^2(V_2)$	9·99	−11·35
	$4d^2$	$d^2(V_2)$	>6·11			$4d^2$	$d^2(V_2)$	>9·39	
	$4s4p$	$sp(V_2)$	~2·15			$4s4p$	$sp(V_2)$	4·49	
Sr	$5p^2$	$p^2(V_2)$	4·45	−0·72	Cd	$5p^2$	$p^2(V_2)$	9·41	−9·90
	$5d^2$	$d^2(V_2)$	>5·69			$5d^2$	$d^2(V_2)$	>8·99	
	$5s5p$	$sp(V_2)$	~2·04			$5s5p$	$sp(V_2)$	4·26	
B	$2s2p^2$	$sp^2(V_1)$	~6·58	−0·30	Ti	$3d^24s^2$	$d^2s^2(V_2)$	0·50	−4·46
	$2s2p3d$	$spd(V_1)$	>8·30			$3d^4$	$d^4(V_2)$	5·35	
	$2s2p^2$	$s^{3/2}p^{3/2}(V_1)$	<6·58		V	$3d^34s4p$	V_5	~5·0	−4·94
Al	$3s3p^2$	$sp^2(V_1)$	~5·03	+2·02		$3d^34s^2$	$d^3s^2(V_3)$	1·47	
	$3s3p3d$	$spd(V_1)$	>5·98			$3d^5$	$d^5(V_5)$	4·04	
	$3s3p^2$	$s^{3/2}p^{3/2}(V_1)$	<5·03		Cr	$3d^44s4p$	V_6	~7·0	−7·25
Ga	$4s4p^2$	$sp^2(V_1)$	~6·15	+2·00		$3d^54s$	$d^5s(V_6)$	1·91	
	$4s4p4d$	$spd(V_1)$	>6·00			$3d^7$	$d^7(V_4)$	5·57	
	$4s4p^2$	$s^{3/2}p^{3/2}(V_1)$	<6·15		Mn	$3d^54s4p$	V_7	~8·0	−7·07
In	$5s5p^2$	$sp^2(V_1)$	~6·30	+2·25		$3d^54s^2$	$d^5s^2(V_5)$	2·21	
	$5s5p5d$	$spd(V_1)$	>5·79			$3d^7$	$d^7(V_7)$	7·52	
	$5s5p^2$	$s^{3/2}p^{3/2}(V_1)$	<6·30		Fe	$3d^64s4p$	V_8	~7·0	−8·08
C	$2s^22p^2$	$s^2p^+p^-(V_2)$	0·32	−19·64		$3d^8$	$d^8(V_2)$	4·8	
	$2s^22p3d^2$	$s^2pd(V_2)$	~9·70		Co	$3d^74s4p$	V_9	~7·0	−8·91
	$2s^23d^2$	$s^2d^2(V_2)$	>11·26			$3d^74s^2$	$d^7s^2(V_3)$	~1—2	
	$2s^22p^2$	$s^{4/3}p^{8/3}(V_2)$	<9·85		Ni	$3d^84s4p$	V_4	~6·0	−9·78
Si	$3s^23p^2$	$s^2p^+p^-(V_2)$	0·21	−8·49		$3d^84s^2$	$d^8s^2(V_2)$	~1—2	
	$3s^23p3d$	$s^2pd(V_2)$	~5·60						

from the results of Shustorovich and Dyatkina;[12] discussion is deferred. It remains now to consider the promotion energies for the valency states required for the σ-bonded structure (*c*). The valency states of the elements of Group I, are identical, of course, with those of the π-complex case. The elements of Group II require a configuration in which the *ns*- and *np*-orbitals are hybridized to give orbitals *ns*/*np* directed towards a localized σ-orbital of a carbon atom. In this case, the electrons occupy singly the above hybrid orbitals and it can be shown that such an arrangement is based on the configuration $sp(V_2)$; the values in Table 1 are taken from Pritchard and Skinner's results.[8] The elements of Group IIIb possess a ground state which is compatible with direct σ-bonding between the central np_σ-orbital and the σ-orbital localized on the carbon atom of the

[12] Shustorovich and Dyatkina, *Zhur. neorg. Khim.*, 1958, **3**, 2721.

cyclopentadienyl system. It is also possible to consider the arrangement $(ns/np)^2(ns/np)^1$, where ns/np denotes a linear hybrid of the ns- and the np-orbital and it can be shown that such an arrangement is based on the configuration $s^{3/2}p^{3/2}(V_1)$. The indices of this configuration will depend on the extent of mixing of the ns- and the np-orbitals in the above hybrids and since we are unable to assess the degree of mixing accurately we assign a promotion energy to the above state as intermediate between that of $s^2p(V_1)$ and $sp^2(V_1)$; the energy is expressed, therefore, as an inequality in Table 1. A similar problem arises with the elements of Group IVb. The ground state $ns^2np^2(V_2)$ is again compatible with direct σ-bonds. Promotion to the configuration $(tr)^1(tr)^1(tr)^2$, where tr denotes a trigonal hybrid, leads to the intermediate configuration $s^{4/3}p^{8/3}(V_2)$. The value listed in Table 1 for the promotion energy to the above valency state is again expressed as an inequality for the same reasons as for Group III.

The calculation of the group overlap integrals for the π-complex is quite straightforward and requires little comment. We have used simple Slater-type atomic orbitals for the central element and calculated the screening constants according to Slater's rules.[13] The bond distances between the ring carbon atoms and the central atom were calculated from the covalent radii of the central elements taken from Pauling's data [14] for twelve-fold co-ordination together with the normal radius of the carbon atom. This procedure is very approximate, but since we are interested only in comparing the values of overlap integrals it seems a consistent method for the calculation of distance. The geometry of the molecule $M(C_5H_5)_2$ or $M(C_5H_5)$ was then calculated with the above M–C distance and with the dimensions of the C_5H_5 ring assumed identical with those of the C_5H_5 ring in ferrocene.[15] The distances in ferrocene and nickelocene are known from accurate X-ray studies, and those of the biscyclopentadienyl compounds from chromium, vanadium, and cobalt are known approximately.[16] The normal parameters p and t which define the overlap integrals [20] are readily calculated and are given in Table 2. The formulæ for the group overlap integrals have been given previously,[3,5,6] but for convenience we list them:

$$S(a_{1g}ns) = \sqrt{10}\cos\theta S(2p_\sigma ns)$$
$$S(a_{1u}np_z) = \sqrt{10}[S(2p_\sigma np_\sigma)\cos^2\theta - S(2p_\pi np_\pi)\sin^2\theta]$$
$$S\begin{pmatrix} e_{1g}nd_{xz} \\ yz \end{pmatrix} = \sqrt{5}[\sqrt{3/2}S(2p_\sigma nd_\sigma)\sin 2\theta\cos\theta + S(2p_\pi nd_\pi)\cos 2\theta\sin\theta]$$
$$S(e_{1u}np_{x,y}) = \sqrt{5}\sin\theta\cos\theta[S(2p_\sigma np_\sigma) + S[2p_\pi np_\pi)]$$

These formulæ apply to $M(C_5H_5)_2$ with D_{5d} symmetry; the five-fold axis of symmetry is the z-axis, and θ denotes the angle between this axis and the metal–carbon vectors. For the monocyclopentadienyl complex, $M(C_5H_5)$, which has only C_{5v} symmetry the g,u classification is removed and it is necessary to divide the above formulæ by $\sqrt{2}$. The formulæ are not corrected for overlap between the π-orbitals of the rings since it is comparative values in which we are interested in this treatment. The majority of the constituent overlap integrals required in the above formulæ have been tabulated,[17,18] but unfortunately, in the case of the integrals $S(2p_\sigma 3d_\sigma)$, $S(2p_\pi 3d_\pi)$ and those involving wave functions of principal quantum number five, the published tables contain intervals in p and t which are often too large for satisfactory interpolation, even for a comparative study. Accordingly, the latter integrals were calculated from the master formulæ for the nearest set of parameters p and t to those calculated above for which the auxiliary functions $A_n(p)$ and $B_n(pt)$ were available. The Swedish tables [19] of $A_n(p)$ for

[13] Slater, *Phys. Rev.*, 1930, **36**, 57.
[14] Pauling, *J. Amer. Chem. Soc.*, 1947, **69**, 542.
[15] Dunitz, Orgel, and Rich, *Acta Cryst.*, 1956, **9**, 373.
[16] Weiss and Fischer, *Z. anorg. Chem.*, 1954, **284**, 69.
[17] Mulliker, Recke, Orloff, and Orloff, *J. Chem. Phys.*, 1949, **17**, 1248.
[18] Jaffé and Doak, *J. Chem. Phys.*, 1953, **21**, 196; Jaffé, *ibid.*, p. 258.
[19] Flodmark, "Table of Molecular A and B Functions," Inst. Theoretical Physics, Stockholm, 1957.

XUM

$m = 0, 1, \ldots 8$ and $0 < p \leqslant 50$ and $B_n(pt)$ for $n = 0, 1, \ldots 8$ and $0 < pt \leqslant 50$ proved invaluable. The integrals involving wave functions of principal quantum number four may be obtained, with one exception, from master formulæ and tables now available

TABLE 2. *Group overlap integrals for systems* $M(C_5H_5)_2$ *and* $M(C_5H_5)$.

M	Electron config.	p	t	$S(a_{1g}ns)$ $[S(a_1ns)]$	$S(a_{1u}np_z)$ $[S(a_1np)]$	$S(e_{1g}nd_{xz})$ $[S(e_1nd)]$	$S(e_{1u}np_{x,z})$ $[S(e_1np)]$
Li	$2p(2s)$	4·987	0·429	0·274	0·201	—	0·229
	$3d$	4·658	0·529	—	—	0·035	—
Na	$3p(3s)$	5·942	0·378	0·205	0·243	—	0·171
	$3d$	4·934	0·660	—	—	0·004	—
K	$4p(4s)$	6·544	0·464	0·072	0·058	—	0·072
	$4d$	5·586	0·715	—	—	−0·009	—
Rb	$5p(5s)$	6·681	0·494	0·027	0·005	—	0·046
	$5d$	5·759	0·733	—	—	−0·007	—
Be	$2s^2$	4·653	0·250	0·606	—	—	—
	$2p^2$	,,	,,	—	0·255	—	0·511
	$3d^2$	3·892	0·494	—	—	−0·112	—
Mg	$3s^2$	5·764	0·262	0·472	—	—	—
	$3p^2$	,,	,,	—	0·261	—	0·345
	$3d^2$	4·868	0·494	—	—	0·095	—
Ca	$4s^2$	6·203	0·357	0·119	—	—	—
	$4p^2$	,,	,,	—	0·053	—	0·151
	$4d^2$	5·363	0·569	—	—	0·009	—
Sr	$5s^2$	6·447	0·390	0·138	—	—	—
	$5p^2$	,,	,,	—	0·111	—	0·136
	$5d^2$	5·619	0·595	—	—	0·030	—
B	$2s2p^2$	4·839	0·111	0·491	0·144	—	0·295
	$2s^23d$	5·129	0·048	0·486	—	−0·080	—
	$(2p^23d)$	3·239	0·660	—	0·191		0·276
Al	$3s3p^2$	5·810	0·163	0·389	0·306	—	0·298
	$3s^23d$	6·038	0·119	0·410	—	−0·063	—
	$(3p^23d)$	4·070	0·660	—	0·337		0·301
Ga	$4s4p^2$	6·127	0·092	0·395	0·304	—	0·313
	$4s^24d$	6·323	0·058	0·414	—	−0·024	—
	$(4p^24d)$	3·901	0·715	—	0·334		0·316
In	$5s5p^2$	6·604	0·130	0·337	0·323	—	0·252
	$5s^25d$	6·810	0·096	0·357	—	−0·018	—
	$(5p^25d)$	4·307	0·733	—	0·354	—	0·257
C	$2s^22p^2$	4·729	0	0·708	0·013	—	0·564
	$2s^22p3d$	4·765	0·018	0·760	0·009	−0·147	0·561
		2·849	0·660				
		5·020	0·058				
	$2s^23d^2$	3·165	0·494		—	−0·298	—
Si	$3s^23p^2$	5·931	0·081	0·619	0·460	—	0·330
	$3s^23p3d$	6·162	0·040	0·627	0·479	−0·059	0·321
		3·861	0·660				
	$3s^23d^2$	4·289	0·494		—	0·009	—
Ge	$4s^24p^2$	6·364	0·031	0·611	0·480	—	0·463
	$4s^24p4d$	6·556	0				
		3·826	0·715	0·624	0·508	−0·037	0·459
	$4s^24d^2$	4·182	0·569		—	−0·068	—
Sn	$5s^25p^2$	6·638	0·070	0·543	0·492	—	0·403
	$5s^25p5d$	6·829	0·040	0·559	0·525	−0·024	0·405
		4·098	0·733				
	$5s^25d^2$	4·453	0·595		—	−0·054	—
Cu	$4p(4s)$	5·077	0·238	0·216	—	—	0·243
	$4d$	3·666	0·715	—	0·021	−0·027	—
Ag	$5p(5s)$	5·332	0·275	0·148	—	—	0·182
	$5d$	3·920	0·733	—	0·010	−0·025	—
Zn	$4p^2(4s^2)$	5·690	0·160	0·468	0·288	—	0·414
	$4d^2$	4·207	0·569	—	—	−0·066	—
Cd	$5p^2(5s^2)$	5·932	0·198	0·350	0·257	—	0·335
	$5d^2$	4·886	0·595	—	—	−0·043	—

as the result of two independent studies of this group.[6,20] The master formula for the one exception, $S(2p_\pi 4d_\pi)$, is derived in the Appendix. The evaluation of the integral

[20] Leifer, Cotton, and Leto, *J. Chem. Phys.*, 1958, **28**, 364.

involving the fourth quantum group is again not always satisfactory from the published tables and the procedure adopted was to evaluate the integral from the master formula for the two nearest and surrounding values of p for which $A_n(p)$ are available, the final integral being then obtained by interpolation. This procedure is different from that employed above since the $A_n(p)$ are tabulated, for non-integral n, over much larger intervals of p than in the case of integral n. In view of the uncertainties in the metal–carbon distances the above procedure seems satisfactory. The values of the group overlap integrals are given in Table 2; the integrals tabulated for the elements of Groups I and III apply, of course, to the monocyclopentadienyl compound and for this reason each column is assigned the two symbols appropriate to D_{5d} or C_{5v} symmetry. For comparison, we give in Table 3 the values of some of the group overlap integrals for the elements of

TABLE 3. *Group overlap integrals for transition elements and Groups* Ib, IIb.
Systems $M(C_5H_5)_2$ and $M(C_5H_5)$.

Element	Principal quantum no. (n)	$S(a_{1g}ns)$	$S[a_{1g}(n-1)d_{z^2}]$	$S[e_{1g}(n-1)d_{xz}]$
Ti				
V		0·266	0·036	0·401
Cr	4	0·283	0·027	0·404
Mn		—	—	—
Fe		0·347	0·011	0·320
C		0·434	0·027	0·243
Ni		0·503	0·027	0·182
Cu	4		—	0·143
Ag	5	—	—	0·338
Zn	4		—	0·128
Cd	5		—	0·247

the first transition series. A rigorous application of Slater's rules has been made for the 3*d*- and 4*s*-orbitals of this group since there is some evidence [21] from spectral parameters that this procedure is justifiable, at least for the free atom.

The calculation of the relevant overlap integrals for a σ-complex is much simpler since overlap now occurs between the 2*s*- and the 2*p*-orbitals of the ring carbon atom and the ns- and the np_σ-orbital of the central atom. We shall not assume that the carbon orbital is a pure tetrahedral hybrid although this is probable, nor shall we consider that the ns- and np-orbitals assume a particular state of hybridization. Instead, the individual overlap integrals, $S(2sns)$, $S(2snp_\sigma)$, $S(2pns)$, $S(2p_\sigma np_\sigma)$ are evaluated as described above and tabulated in Table 4. For the σ-bonded model, we have calculated the interatomic distances from Pauling's single-bond covalent radii, except for the first transition series where, for the direct comparison with the known π-complex structure, the distance was taken as identical with that observed in the π-complex. We have not attempted to calculate overlap integrals involving atomic orbitals of principal quantum six, although the method used by Brown [6] and by Leifer *et al.*[20] is equally applicable to this group.

Craig *et al.* considered the overlap criterion to be a better measure of interaction between two orbitals than the maximum extension of a given orbital.[23] Nevertheless, it provides no direct estimate of the *energy* of interaction of two orbitals; in general, theory is incapable of determining this energy. We are forced to rely on the overlap integral as a measure of chemical bonding, and these rather unsatisfactory foundations render it unwise to theorise too extensively; nevertheless, it is reasonable to suppose that trends in the overlap integrals should reveal trends in bond character, provided that the differences are considerable. With this qualification we shall now consider the results tabulated.

[21] Brown, *J. Chem. Phys.*, 1958, **28**, 67.
[23] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332.
[23] Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, New York, 1944, p. 76.

XUM

It follows from the extremely small values of the integral $S(e_1nd)$ (Table 2) that promotion to valency states involving outer *d*-orbitals is not likely to lead to appreciable bonding for elements in the Group Ia, IIa, IIIb, or IVb. This conclusion is supported by the relatively large promotion energies (Table 1) for the corresponding valency states of these elements. It at once differentiates these elements from those of the first transition series

TABLE 4. *Constituent overlap integrals for σ-bonded systems* $M(C_5H_5)_2$ and $M(C_5H_5)$.

Element	*n*	*p*	*t*	$S(2sns)$	$S(2snp_\sigma)$	$S(2p_\sigma ns)$	$S(2p_\sigma np_\sigma)$
Li	2	4·535	0·429	0·333	0·477	0·153	0·187
Na	3	5·146	0·378	0·308	0·458	0·098	0·112
K	4	5·726	0·464	0·241	0·345	0·120	0·022
Rb	5	6·000	0·494	0·186	0·296	0·005	−0·003
Be	2	4·618	0·250	0·341	0·463	0·253	0·272
Mg	3	5·766	0·262	0·292	0·430	0·160	0·208
Ca	4	6·200	0·357	0·246	0·381	0·080	0·105
Sr	5	6·450	0·390	0·221	0·348	0·053	0·070
B	2	4·660	0·111	0·365	0·430	0·332	0·308
Al	3	5·810	0·163	0·294	0·417	0·208	0·269
Ga	4	6·102	0·092	0·307	0·444	0·213	0·261
In	5	6·438	0·130	0·291	0·431	0·174	0·228
C	2	4·729	0·000	0·341	0·368	0·368	0·329
Si	3	5·514	0·080	0·322	0·395	0·265	0·304
Ge	4	5·926	0·031	0·331	0·447	0·253	0·251
Sn	5	6·229	0·070	0·245	0·448	0·210	0·262
Cu	4	5·084	0·238	0·355	0·513	0·123	0·117
Ag	5	5·325	0·275	0·319	0·469	0·080	0·079
Zn	4	5·558	0·160	0·344	0·481	0·178	0·195
Cd	5	5·947	0·198	0·316	0·475	0·138	0·182
Ti	4	—	—	—	—	—	—
V	4	5·470	0·292	0·181	0·457	0·099	0·112
Cr	4	5·363	0·271	0·326	0·478	0·107	0·118
Mn	4	—	—	—	—	—	—
Fe	4	5·062	0·232	0·362	0·516	0·134	0·125
Co	4	5·391	0·213	0·344	0·493	0·141	0·151
Ni	4	5·654	0·195	0·332	0·474	0·156	0·179

for which the integral $[S(e_{1g}3d)]$ is the primary bonding interaction and is of reasonable magnitude throughout the series (Table 3). The relative inefficiency of *d*-orbital overlap in these groups, compared with those of the transition elements, is due to the greater screening of *d*-electrons by the remaining electrons.

In contrast, the integral $S(e_{1u}np)[S(e_1np)]$ is of reasonable size for most of the members of the above groups and, taken together with the lower promotion energies of the required valency state, indicates that it is the *np*-orbitals which will be responsible for any covalent bonding on the π-complex model for the cyclopentadienyl compounds of the elements of these groups.

Moreover, for all the elements considered in Table 2 there is a decrease in a given overlap integral on descent of a given Periodic Group, particularly for the elements of Groups Ia and IIa. It follows that increased ionic character will be expected for a given complex on increasing the atomic number of the central atom; a conclusion consistent with experiment.

From Table 4, it is noticeable that in general the admixture of the np_σ-orbital with the *ns*-orbital of the central atom leads to increased overlap with the carbon 2*s*- and 2*p*-orbitals; however, there are some exceptions. It follows that *s*/*p* hybridization of the central atom will lead to increased overlap, but that the extent of hybridization may well vary considerably within the groups under consideration. Finally, in the formation of a σ-complex a cyclopentadienyl radical (configuration $a_1^2e_1^3$) is converted into a system in which conjugation is limited to only four carbon atoms. The loss in conjugation energy per ring is about 1·4β, on the simple Hückel molecular-orbital theory, where β

XUM

is the resonance integral between adjacent carbon $2p^{\pi}$-orbitals. In other words, where the σ- and the π-model appear to be of very similar stability, the above effect may be especially important.

After the above general conclusions we shall discuss the known cyclopentadienyl complexes of these groups in terms of the theoretical results given in Tables 1—4.

Group I.—All the alkali metals, except francium, are known to form cyclopentadienyl compounds $M(C_5H_5)$. Columns 5 and 10 of Table 1 show that the transfer of an electron from an alkali metal to a cyclopentadienyl radical is energetically favoured and we should expect, therefore, that these compounds will be largely ionic in character owing mainly to the low first ionization potentials of the alkali metals. However, the promotion energy of the *ns*-electron to an np_{σ}-orbital is quite low and the overlap integrals on both σ- and π-complex models are considerable, at least for the early members of the Group, and so some covalent character is indicated for monocyclopentadienyl-lithium and -sodium. It is impossible to conclude with our approximations which of the two models is to be preferred for covalent bonding. Experimentally,[4] it is found that these compounds are colourless salts which decompose immediately in air but dissociate in polar solvents. The sodium compound has been estimated to possess 50% ionic character.[24]

The subgroup elements, copper and silver, might be expected to form complexes exhibiting some ionic character in view of the results given for these elements in Table 1; the formation of ions is possible on energetic considerations. The covalent π-complex model shows quite reasonable overlap for the quantity $S(e_1np)$ but considerable overlap also occurs of the type $S[e_1(n-1)d]$ between the filled $(n-1)d$-orbitals of these elements and the e_1-cyclopentadienyl orbitals. Thus both bonding and anti-bonding interactions will occur between the e_1-orbital and the orbitals of the central atom; this is likely to render the complex unstable. The covalent σ-complex model suffers no such disadvantage and exhibits overlap integrals of reasonable magnitude (Table 4); moreover the promotion energies are fairly small and, indeed, *s*/*p* hybridization would lower these energies. It follows then that we should predict the monocyclopentadienyl compounds of Group Ib to show some ionic character but to be largely σ-bonded and covalent in structure. To date, no simple cyclopentadienyl complex of this subgroup has been obtained but copper(I) yields the white, crystalline cyclopentadienyl triethylphosphine complex C_5H_5Cu,PEt_3, which is stable to water and is apparently a σ-bonded complex.

Group II.—Of the main-group elements, beryllium, magnesium, and calcium form dicyclopentadienyl compounds.[25-27] It follows from our measure of ionic character that considerable energy is required for the transfer of electrons from the central atom to the cyclopentadienyl radicals. This quantity decreases markedly down the Group and only for the beryllium complex does ionic character appear to be really improbable. Both covalent π- and σ-complex models show considerable overlap which decreases down the series; however, such overlap is achieved by the π-model at the expense of considerably more promotion energy (p^2V_2) than in the σ-model case (spV_2). It is tempting to conclude that for the higher members of this group the σ-complex is the more likely, but this is not necessarily correct, for the following reasons. First, there is loss of resonance energy of the cyclopentadienyl rings on σ-complex formation and, secondly, there is additional stabilization for the π-complex model of the type $(a_{1g}ns)$ which, as column 5 of Table 2 indicates, is considerable. These additional factors which increase the stability of the π-complex make the position ambiguous; we shall note similar ambiguity for Group III. It follows from our theoretical considerations that the calcium complex will be largely ionic, the magnesium complex ionic with some covalent character, and the beryllium complex mainly covalent; it is difficult to predict which of the covalent models will be favoured

[24] Weise and Cohen, *Chem. Abs.*, 1957, **51**, 8664.
[25] Fischer and Hofmann, *Chem. Ber.*, 1959, **92**, 482.
[26] Cotton and Wilkinson, *Chem. and Ind.*, 1954, 307.
[27] Ziegler and Froitzheim, *Chem. Ber.*, 1956, **89**, 434.

XUM

although it appears that where ionic character is most unlikely the σ-bonded structure is the more probable since the difference in promotion energies is then greater. The beryllium compound [25] is a white compound, easily hydrolysed and oxidized, and has a finite dipole moment; Fischer and Hofmann suggested that it is a genuine σ-complex. The magnesium compound [26] appears to possess a sandwich structure both in the vapour state and in solution, as shown by the infrared spectrum and zero dipole moment; it is generally regarded as an ionic compound but since the overlap integrals on both σ- and π-models † are considerable some covalent contribution is to be expected. The calcium compound [27] has not been obtained pure.

In the subgroup of Group II both zinc and mercury form biscyclopentadienyl compounds. Columns 5 and 10 of Table 1 show that ionic compounds are most unlikely in view of the large energies involved. The covalent π-complex model is again improbable for reasons analogous to those given for Group Ib, namely, that although the overlap integral $S(e_{1u}np)$ (Table 2) is of reasonable magnitude so too is the integral $S[e_{1g}(n-1)d]$ (Table 4). It follows that the bonding interactions of the former type will be counteracted by the anti-bonding interactions of the latter type owing to the completely filled $(n-1)d$ orbitals. Again the σ-complex possesses no such disadvantages and we should predict, therefore, that zinc and mercury will form σ-complexes, especially in view of the much lower valency-state promotion energies involved $[sp(V_2) < p^2(V_2)]$. It is observed that both biscyclopentadienyl-mercury and -zinc are relatively unstable; the infrared spectrum of the former is most consistent with a σ-complex structure.[28]

Group III.—The elements indium and thallium form monocyclopentadienyl compounds [29] of the type $M(C_5H_5)$ although indium also forms an intermediate $In(C_5H_5)_3$ which on being heated decomposes to give the mono-complex. Table 1 indicates that the formation of ionic compounds is energetically possible for all the members of the group. The π-complex model, however, indicates considerable overlap (Table 2) for most of the members of Group III so that some covalent character cannot be excluded. With the electron configuration ns^2np^1, both bonding (e_1np) and anti-bonding $(a_1ns)^*$ types of interaction will occur, whereas promotion to the valency state $(sp)^0(sp)^2(sp)^1$, in which sp denotes linear hybrids directed towards and away from the ring, should lead to completely bonding interactions. The use of the latter valency state requires, however, considerable promotion energy as shown by the inequalities in Table 1. In contrast, the σ-model may be based on direct interaction between the $np\sigma$-orbital of the central atom and a carbon σ-orbital of the ring; in this case the valency state will lie close to the ground state with a relatively low promotion energy. However, as in Group II the σ-complex is formed at the expense of ring conjugation energy and without the additional stabilization of the a_1-orbital which occurs with the π-complex formed from the second valency state above. The situation is again ambiguous. If the sum of the loss in conjugation energy and the stabilization of the a_1-orbital is greater than the difference in promotion energies between the valency states appropriate to the σ- and the π-model, then the π-complex will be favoured as the covalent structure. Experimentally, it is found that both the indium and the thallium compound are insoluble in water and that the indium is more readily oxidised than the thallium compound. It now seems well established that the thallium compound possess C_{5v} symmetry since the microwave spectrum [30] of the vapour gives unequivocal proof of this and also leads to a Tl–C bond distance of about 2·4 Å. It was suggested by Cotton and Reynolds [5] that the thallium complex was largely ionic, but this was due to a numerical error † and the correct values given in Table 2 show some

† Dr. Cotton, in a personal communication, has informed the author that the data in ref. 8 are incorrect because of a numerical error.

[28] Piper, Hafner, and Wilkinson, *J. Inorg. Nuclear Chem.*, 1956, **2**, 82.
[29] Fischer and Hofmann, *Z. angew. Chem.*, 1957, **69**, 639.
[34] Meister, *ibid.*, p. 533.
[30] Tyler, Cox, and Sheridan, *Nature*, 1959, **183**, 1182.

XUM

covalent bonding for both monocyclopentadienyl-indium and -thallium. It is implicit in the above argument of course that the overlap integrals for the thallium complex will be only slightly smaller than those calculated for the indium complex. The additional fact that the thallium compound is stable in the vapour phase at 100° seems to suggest some covalent character in the molecule.

Group IV.—Tin and lead form biscyclopentadienyl compounds.[31] The energies required for the formation of ions (columns 5 and 10, Table 1) indicate that ionic character is not likely to be important in this Group, in contrast to Group III. The symmetrical π-complex (D_{5d}) is also unlikely. The bonding effect which arises from the overlap between the half-filled cyclopentadienyl (e_{1u}) orbitals with the singly occupied p_xp_y-orbitals of the central atom will be offset by the anti-bonding effect of overlap of the filled a_{1g} cyclopentadienyl orbitals with the filled *ns*-orbital of the central atom; Table 2 indicates that both interactions are considerable for the elements of Group IV. It follows that the D_{5d} model is unlikely. It has recently been suggested [32] that an angular sandwich model may occur in this Group; the central atom is considered to be in a valency state $(nsnp^2)^1(nsnp^2)^1(nsnp^2)^2$ with overlap between the singly occupied trigonal hybrids and the symmetric cyclopentadienyl a_1-orbitals. This model requires both promotion of the π-electrons of the cyclopentadienyl ring to the state $a_1e_1^4$ and considerable promotion of the central atom to the above valency state (Table 1). In contrast, direct σ-bonding is possible on the basis of the ground-state configuration, $s^2p^+p^-(V_2)$, of the central atom, and the overlap integrals are of reasonable magnitude (Table 4). It is, of course, possible that some mixing of the *s*- and *p*-orbitals of the central atom may occur, with a consequent increase in promotion energy, and the observed dipole moments suggest that this is so. The experimental evidence is not yet unambiguous, as admitted by Dave *et al.*;[32] the interpretation of the nuclear magnetic resonance spectrum does not rule out the σ-complex, and the infrared spectrum provides the sole evidence for the angular π-complex.

First Transition Series.—Table 1 shows that, with the possible exception of titanium and vanadium, considerable energy is required for the formation of an ionic compound. The promotion energies listed for the valency states appropriate to the π-complex are taken from the calculations of Shustorovich and Dyatkina [12] and the wide range of some of them merits comment. Unfortunately, there is considerable uncertainty in the nature of the valency state of the central metal atom in the biscyclopentadienyl compounds of the transition elements, as it is difficult to assess the degree of mixing of the 3*d*- and 4*s*-orbitals. If the configuration $3d^n$ is chosen, thereby leaving the 4*s*-orbital empty but involving considerable promotion energy, a stable bonding interaction of the type $(a_{1g}4s)$ will occur throughout the series (compare overlap integrals in Table 3). However the configuration $3d^{n-2}4s^2$, requiring a much lower promotion energy (as given by the lower limit in Table 1), leads to anti-bonding interactions $(a_{1g}4s)^*$, and not simply to the absence of the above bonding $(a_{1g}4s)$ as suggested by the Russian workers.

The group overlap integrals for the π-complex are similar throughout the series, on the assumption that Slater's rules are applicable. The possible σ-complex, although having reasonable overlap integrals, requires promotion energies that are always greater than for the π-model. From this difference and from the loss of ring conjugation energy on σ-complex formation it follows that the π-complex model is generally to be preferred to the σ-complex for the biscyclopentadienyl compounds of the transition metals. As suggested by Shustorovich and Dyatkina,[12] ionic character is especially likely for the manganese compound in view of the exceptionally large upper limit to the range of promotion energies. The titanium, vanadium, and chromium compounds may also be expected to show some ionic character in view of the similarity of the promotion energies

[31] Fischer and Grubert, *Z. Naturforsch.*, 1956, **11**b, 423; *Z. anorg. Chem.*, 1956, **286**, 237.
[32] Dave, Evans, and Wilkinson, *J.*, 1959, 3684.

to the energy of electron transfer: in fact, both the vanadium and the chromium compound form ammoniates and with ferrous chloride in tetrahydrofuram yield ferrocene.[4]

This comparison between the compounds of the transition metals and of the elements of Groups I—IV, showing that promotion energies of the former on the π-complex model are always lower than those on the σ-complex model, has allowed a fairly secure theory to be constructed for the transition series. However, no such clear difference exists for elements of Groups I—IV and it is harder to predict the type of covalent complex most likely for a given Group.

Conclusions.—Our general conclusions may be summarised as follows: Groups Ia and IIa, especially the lower members, will exhibit pronounced ionic character. Groups Ib and IIb will tend to form σ-bonded complexes. Group IIIb will form complexes of mixed ionic–covalent character, and probably of π-complex type. Group IV will form neither ionic nor simple π-complexes, but the structure of the covalent complex is probably based on the σ-model. The experimental evidence is still not clear.

Appendix

Evaluation of Overlap Integral $S(2p_\pi 4d_\pi)$.—We use the functions:

$$\psi_{2p_\pi} = \frac{(\alpha_A)^{5/2}}{(\pi)^{1/2}} \cdot r_A \exp(-\alpha_A r_A) \sin\theta_A \cos\phi$$

$$\psi_{4d_\pi} = \frac{(2\alpha_B)^{4\cdot2}}{(4\pi)^{1/2}} \cdot \frac{(15)^{1/2}}{(7\cdot4!)^{1/2}} \cdot r_B{}^{2\cdot7} \exp(-\alpha_B r_B) \sin\theta_B \cos\theta_B \cos\phi$$

With the usual notation for the evaluation of overlap integrals [17] and on transformation to spheroidal co-ordinates ζ, η, and ϕ we obtain the expression:

$$S(2p_\pi 4d_\pi) = N_{24} \int_1^\infty \int_{-1}^{+1} (\zeta - \eta)^{1\cdot7}(\zeta + \eta)(\zeta\eta - 1)(\zeta^2 - \zeta^2\eta^2 + \eta^2 - 1)\, e^{-p\zeta} e^{-pt\eta} d\zeta d\eta$$

where $N_{24} = p^{6\cdot7}(1 + t)^{2\cdot5}(1 - t)^{4\cdot2}(15)^{1/2}/2^{3\cdot5}(7\cdot4!)^{1/2}$

On expansion of the above expression and term-by-term integration we obtain the final expression:

$$N_{24} \sum_{i=0}^{\infty} \binom{1\cdot7}{i}(-1)^i[(A_{5\cdot7-i} - 2A_{3\cdot7-i} + A_{1\cdot7-i})(B_{i+1} - B_{i+3}) + (A_{4\cdot7-i} - A_{2\cdot7-i})(2B_{2+i} - B_{4+i} - B_i)]$$

$$A_n(p) = \int_1^\infty x^n e^{-px} dx$$

$$B_m(pt) = \int_{-1}^{+1} x^m e^{-ptx} dx$$

The numerical values of these functions are available from Flodmark's tables.[19]

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XUM

140. *The Chemistry of Extractives from Hardwoods. Part XXXI.* 2-Acetyl-1,8-dihydroxy-3-methylnaphthalene (Musizin), a Constituent of* Maesopsis eminii.

By C. J. Covell, F. E. King, and J. W. W. Morgan.

The heartwood of *Maesopsis eminii* contains a new phenolic compound (musizin) which can be extracted with light petroleum and has been identified as 2-acetyl-1,8-dihydroxy-3-methylnaphthalene.

Musizi is an African timber derived from the tree *Maesopsis eminii*. Although not classified as resistant, at least two well-defined phenolic compounds are present in the heartwood, a quantity of which was made available for our examination by Dr. R. H. Farmer, Forest Products Research Laboratory, Princes Risborough. The first of these (musizin) is present in the highly coloured product from extraction with boiling light petroleum. A second compound (maesopsin) can be obtained by further treatment of the wood with acetone, and will be described later. Both products appear to be concentrated in the outer heartwood zone, extraction of the inner heartwood giving no musizin and diminished yields of maesopsin.

Musizin has the molecular formula $C_{13}H_{12}O_3$. It is bright yellow and its solubility in aqueous bases and ferric chloride reaction indicate its phenolic nature. The formation of a diacetate, dibenzoate, and of a dimethyl ether with dimethyl sulphate show that there are two hydroxyl groups. Although musizin does not form carbonyl derivatives the remaining oxygen atom is part of a keto-group, since musizin dimethyl ether exhibits the infrared absorption peak at 1702 cm.$^{-1}$ of a conjugated aromatic carbonyl group. When fused with alkali musizin yields a dihydric phenol, $C_{11}H_{10}O_2$, characterised as diacetate and dibenzoate, which must therefore arise from the loss of an acetyl side-chain. The evidence is consistent with its formulation as a derivative of methylnaphthalene and confirmation was obtained by distillation of the product with zinc dust, whereupon 2-methylnaphthalene was isolated. The ultraviolet absorption of the C_{11} phenol resembles that of 1,8-dihydroxynaphthalene [1,2] and the assignment of the hydroxyl groups to the *peri*-position was endorsed by the ability of the phenol to increase the acidity of a boric acid solution,[2] the change in pH being comparable with that caused by the addition of 1,8-dihydroxynaphthalene (see Table).

Compound	pH of boric acid soln.	pH after addition	ΔpH	Compensated ΔpH
Ethanol (blank)	4·13	4·53	+0·40	—
β-Naphthol	4·11	4·50	+0·39	−0·01
Sorbitol	4·03	3·59	−0·44	−0·84
t-Butylcatechol	4·08	3·81	−0·27	−0·67
1,8-Dihydroxynaphthalene	3·96	2·02	−1·94	−2·34
Dihydroxymethylnaphthalene from alkali fusion	3·90	2·12	−1·78	−2·18

2 ml. of a 0·1M-ethanolic solution of each of the above compounds were added to 5 ml. of 0·5M-aqueous boric acid. The effect of the solvent is allowed for in the compensated ΔpH.

As with other 1,8-dihydroxynaphthalenes [2,3] reaction with diazomethane gave a monomethyl ether, and as this proved to be identical with a synthetic specimen of 1-hydroxy-8-methoxy-3-methylnaphthalene † the constitution of the product of zinc-dust distillation was thereby established as 1,8-dihydroxy-3-methylnaphthalene.

As a preliminary step in determining the position of the acetyl group, musizin was

* Part XXX, *J.*, 1960, 4738.

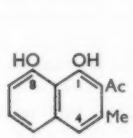
† Unpublished work by Dr. W. B. Whalley to whom the authors are indebted for a sample.

[1] Daglish, *J. Amer. Chem. Soc.*, 1950, **72**, 4859.

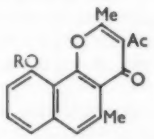
[2] Hochstein, Stephens, Conover, Regna, Pasternack, Gordon, Pilgrim, Brunings, and Woodward, *J. Amer. Chem. Soc.*, 1953, **75**, 5455.

[3] Böeseken and Smitt, *Rec. Trav. chim.*, 1939, **58**, 125.

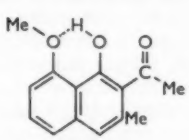
treated with alkaline hydrogen peroxide.[4] The sole isolable product was 3-hydroxyphthalic acid, whence the acetyl group is located in the ring bearing the *C*-methyl group, at either the 2- or 4-position. The marked chelation revealed by the occurrence of the carbonyl absorption peak at 1630 cm.$^{-1}$ strongly suggests that the acetyl substituent is at the 2-position adjacent to a hydroxyl group.[5] Furthermore musizin forms at low temperatures a complex with boroacetic anhydride which on decomposition with water gives a yellow monoacetate,[6] further acetylated to the diacetate. The monoacetate has the properties expected for an *o*-hydroxycarbonyl compound, gives a green colour with ferric chloride, and has infrared absorption bands at 1750 cm.$^{-1}$ (acetate carbonyl) and 1625 cm.$^{-1}$ (chelated nuclear acetyl). At higher temperatures boroacetic anhydride protects the two *peri*-hydroxyl groups and nuclear acetylation occurs. This is again apparent from the infrared absorption of the yellow crystalline product obtained on decomposition of the complex, which has bands at 1685 cm.$^{-1}$ (unchelated nuclear acetyl) and 1625 cm.$^{-1}$ (chelated nuclear acetyl), and from the formation of an *OO*-diacetate on further acetylation. Musizin is accordingly 2-acetyl-1,8-dihydroxy-3-methylnaphthalene (I).



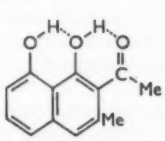
(I)



(II)



(III)



(IV)

Final proof that the acetyl side-chain is *ortho* with respect to the 1-hydroxyl group came from the preparation of the naphthopyrone (II; R = Ac) by the prolonged action of sodium acetate and acetic anhydride. Musizin is therefore a further example of the group of natural products based on 1,8-dihydroxy-3-methylnaphthalene, which include splumbagin,[7] 7-methyljuglone,[7] and diospyrol.[8] Treatment of musizin with diazomethane affords two isomeric monomethyl ethers, both of which give musizin on demethylation and musizin dimethyl ether when further methylated with methyl sulphate–potassium carbonate. However, neither product exhibits the ferric reaction nor the displacement of the infrared carbonyl absorption to 1630 cm.$^{-1}$ that would be expected for the 8-*O*-methyl isomer. In fact, the infrared carbonyl absorption of each compound (1686 and 1694 cm.$^{-1}$, respectively) is normal for an unchelated aromatic carbonyl group. The respective constitutions of the two ethers can be inferred from the action of sodium acetate and acetic anhydride. Under the conditions used to form a naphthopyrone with musizin, both compounds gave normal acetates, but at higher temperatures whereas 1-*O*-methylmusizin again yielded a normal acetate 8-*O*-methylmusizin was converted into the naphthopyrone (II; R = Me). The failure of 8-*O*-methylmusizin (III) to exhibit chelation can be attributed to hydrogen bonding between the 1-hydroxyl group and the 8-oxygen atom, an effect which may also be responsible for the characteristic monomethylation of 1,8-dihydroxynaphthalene derivatives with diazomethane. In musizin itself hydrogen bonding is possible between the two hydroxyl groups and also between the 1-hydroxyl and the acetyl substituent, as in (IV). It is noteworthy that in the methylation of musizin by diazomethane the 1-*O*-methyl isomer preponderates, which may in part be due to the activating effect of the carbonyl group.[9,10]

[4] Dieterle and Kruta, *Arch. Pharm.*, 1936, **274**, 457.
[5] Hunsberger, *J. Amer. Chem. Soc.*, 1950, **72**, 5626.
[6] Dimroth, *Annalen*, 1926, **446**, 97.
[7] R. H. Thomson, "Naturally Occurring Quinones," Butterworth's Scientific Publications, London, 1957, pp. 96, 97.
[8] Loder, Mongolsuk, Robertson, and Whalley, *J.*, 1957, 2233.
[9] Geissman and Hinreiner, *J. Amer. Chem. Soc.*, 1951, **73**, 782.
[10] Haber, Nikuni, Schmid, and Yagi, *Helv. Chim. Acta*, 1956, **39**, 1654.

XUM

Experimental

Unless otherwise stated melting points are uncorrected and light petroleum (b. p. 60—80°) was used; ether solutions were washed with water and dried over magnesium sulphate.

Musizin.—The comminuted heartwood (2·5 kg.) of *Maesopsis eminii* was extracted for 18 hr. with boiling light petroleum in a continuous-return apparatus. The solution obtained was evaporated to a red powder (16 g.) which was dissolved in ether (1600 ml.) and extracted with 5% aqueous sodium carbonate (500 ml.). The aqueous extracts on acidification deposited a bright yellow solid (6·4 g.) which crystallised from light petroleum in yellow needles of *musizin*, m. p. 164—165° (evac. tube) (Found: C, 72·1; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%); $\lambda_{max.}$ in light petroleum, 219, 266, 402 mμ (log ε 4·17, 4·39, 3·68); infrared band in chloroform at 1630 cm.$^{-1}$ which was not displaced on dilution of the sample. Musizin was insoluble in aqueous sodium hydrogen carbonate, soluble in sodium carbonate, and gave a green colour with ferric chloride solution; its solution in hot methanol rapidly discoloured and on cooling dark brown crystals were obtained.

With boiling acetic anhydride and pyridine musizin afforded a *diacetate*, m. p. 189—190° (Found: C, 67·7; H, 5·3. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%) [$\lambda_{max.}$ in ethanol 225, 286, and 324 mμ (log ε 4·82, 3·80, 3·13)], obtained as prisms from ethanol or acetic acid, and with boiling benzoyl chloride–pyridine *a dibenzoate*, m. p. 187—188° (Found: C, 76·5; H, 4·9. $C_{27}H_{20}O_5$ requires C, 76·4; H, 4·8%), was obtained which crystallised from ethanol as fine needles.

Musizin Dimethyl Ether.—Musizin (2 g.) and dimethyl sulphate (6 ml.) in boiling acetone (150 ml.) were stirred with anhydrous potassium carbonate (20 g.) for 2 hr. The solution was then filtered, concentrated, and treated with concentrated ammonia and the product, precipitated with water, was collected in ether. Evaporation of the ether solution gave a brown syrup which was purified by filtering a benzene solution through alumina. The filtrate afforded a colourless syrup (1·65 g.) which crystallised from light petroleum as prisms of *musizin dimethyl ether*, m. p. 77—81° [Found: C, 73·5; H, 6·6; OMe, 24·4%; *M* (Rast), 289. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6; OMe, 25·4%; *M*, 244]; infrared band in carbon tetrachloride at 1702 cm.$^{-1}$. Repeated crystallisation did not narrow the melting range.

The dimethyl ether (0·5 g.) was heated with pyridinium chloride (1·5 g.) for 30 min. at 200—210°.[11] The melt was digested with water; the precipitated solid when recrystallised from light petroleum gave musizin (0·28 g.), m. p. 162—163° (evac. tube).

Alkali Fusion of Musizin.—Musizin (2 g.), sodium hydroxide (3 g.), potassium hydroxide (3 g.), and water (6 ml.) were fused at 200—210° under a stream of nitrogen, and the melt was kept at this temperature for 15 min. Water was added to the cooled mixture, and the solution obtained was acidified, precipitating a brown solid which was collected in ether solution. Evaporation of the ether solution afforded a red solid which crystallised from water as feathery buff-coloured crystals (1 g.), m. p. 135—138°. Recrystallisation from light petroleum (b. p. 80—100°) gave almost colourless crystals of 1,8-*dihydroxy*-3-*methylnaphthalene*, m. p. 140—141° (Found: C, 75·5; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·8%); $\lambda_{max.}$ in ethanol 231, 307, 322, 336 mμ (log ε 4·83, 3·87, 3·92, 4·01). 1,8-Dihydroxynaphthalene, prepared by alkali fusion of sodium 8-hydroxynaphthalene-1-sulphonate, had $\lambda_{max.}$ 227, 305, 320, 335 mμ (log ε 4·73, 3·83, 3·87, 3·96).

By the action of boiling acetic anhydride and pyridine a *diacetate*, m. p. 117—118° (Found: C, 69·9; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·7; H, 5·5%), was obtained which crystallised from light petroleum, and boiling benzoyl chloride and pyridine gave needles from ethanol of a *dibenzoate*, m. p. 192° (Found: C, 78·4; H, 4·8. $C_{25}H_{18}O_4$ requires C, 78·5; H, 4·7%).

Zinc-dust Distillation of 1,8-*Dihydroxy*-3-*methylnaphthalene.*—An intimate mixture of the dihydroxymethylnaphthalene (0·32 g.) and purified zinc dust (15 g.) [3] was put in a tube and covered with a further 15 g. of zinc dust. With a current of hydrogen passing through it, the tube was gradually heated to red heat. The distillate was purified by passing a solution in light petroleum through alumina. The evaporated eluate gave 2-methylnaphthalene (0·06 g.), m. p. 25—28° (picrate, m. p. 114—115° undepressed by an authentic sample of 2-methylnaphthalene picrate, m. p. 115—116°).

Methylation of 1,8-*Dihydroxy*-3-*methylnaphthalene.*—Excess of diazomethane in ether (30 ml.) was added to a solution of the dihydroxymethylnaphthalene (0·4 g.) in ether (20 ml.) which

[11] Prey, *Ber.*, 1941, **74**, *B*, 1219.

was then kept at 0° for 1 hr. Evaporation of the solvent afforded an orange oil which was purified by chromatography in light petroleum on silica. First fractions yielded crystals (0·22 g.), m. p. 85—90°, which discoloured on exposure to the air. Recrystallisation from light petroleum gave needles of *1-hydroxy-8-methoxy-3-methylnaphthalene*, m. p. 92—93° (Found: C, 76·5; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). This compound did not depress the melting point of a synthetic sample, m. p. 91—93°, kindly supplied by Dr. W. B. Whalley.[12] The compound was insoluble in cold or hot aqueous sodium hydroxide but dissolved in aqueous ethanolic sodium hydroxide.

Oxidation of Musizin by Alkaline Hydrogen Peroxide.—Musizin (1 g.) was dissolved in aqueous sodium hydroxide (40 ml.; 2N), and hydrogen peroxide (20 ml.; 100 vol.) was added. After the initial reaction had subsided the mixture was heated at 100° for 30 min. The solution was acidified and extracted with ether, the extracts yielding a yellow syrup which was chromatographed in benzene–ether (20 : 1) on silica. Elution by benzene–ether (10 : 1) gave 3-hydroxyphthalic acid (0·21 g.), m. p. 168—169° (evac. tube) resolidifying and melting again at 200—201° (Found: C, 52·5; H, 3·3. Calc. for $C_8H_6O_5$: C, 52·7; H, 3·3%). 3-Hydroxyphthalic acid has recorded m. p. 166—167° and the anhydride m. p. 199—201°.[13]

Methylation of the 3-hydroxyphthalic acid isolated in this work and of a sample of crude dimethyl 3-hydroxyphthalate kindly supplied by Prof. A. W. Burgstahler [14] gave identical samples of dimethyl 3-methoxyphthalate, m. p. 75—76°.

Action of Boroacetic Anhydride on Musizin.—(*a*) *At* 45—50°.[6] Musizin (0·5 g.), boroacetic anhydride (0·5 g.), and acetic anhydride (3 ml.) were heated at 45—50° for 90 min. The mixture was kept at room temperature overnight and then hydrolyzed by pouring it into hot water. The precipitate was collected and leached with boiling light petroleum (b. p. 80—100°) leaving a red residue. The filtered petroleum solution, on cooling, gave yellow needles (0·11 g.) of *8-O-acetylmusizin*, m. p. 128—129° (Found: C, 69·7; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%). The compound gave a green colour with ferric chloride in methanol and displayed intense infrared bands in chloroform at 1750 and 1625 cm.$^{-1}$. A weak band at 1685 cm.$^{-1}$ was attributed to impurity. The red petroleum-insoluble residue, after hydrolysis by ethanol, afforded unchanged musizin.

Acetylation of the above monoacetate by boiling acetic anhydride and pyridine gave musizin diacetate, m. p. 182—185°, after two recrystallisations from ethanol; mixed m. p. with authentic sample 186—189°.

(*b*) *At* 100°. A mixture of musizin (0·5 g.) boroacetic anhydride (0·5 g.), and acetic anhydride (2·5 ml.) was heated to 100° during 45 min., and kept thereat for another 75 min. before being decomposed with boiling water. After the mixture had cooled, a greenish-yellow solid was filtered off and repeatedly extracted with boiling light petroleum (b. p. 80—100°). The concentrated extract, on cooling, afforded yellow plates (0·21 g.) of a *C-acetylmusizin*, m. p. 204—205° (Found: C, 69·3; H, 5·3. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%); infrared bands in chloroform at 1685 and 1625 cm.$^{-1}$. The compound gave a green colour with ferric chloride.

C-Acetylmusizin (0·10 g.) treated with boiling acetic anhydride and pyridine for 10 min. afforded a *diacetate* (0·09 g.), m. p. 168—169° (Found: C, 66·7; H, 5·2. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%), as blades from ethanol.

Naphthopyrone Derivative of Musizin.—Musizin (0·2 g.), fused sodium acetate (0·5 g.), and acetic anhydride (5 ml.) were boiled under reflux for 18 hr., and the mixture was then poured on crushed ice. The solid obtained was recrystallised from acetic acid and then ethanol to give cream-coloured needles of the *naphthopyrone derivative* (II; R = Ac), m. p. 198—199° (Found: C, 70·3; H, 5·2. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%); $\lambda_{max.}$ in ethanol 225, 251, 304, 339, 354 mμ (log ε 4·90, 4·93, 3·80, 3·64, 3·64). Under the above conditions 1,8-dihydroxynaphthalene gave its normal diacetate, m. p. 151—153°.

Musizin Monomethyl Ethers.—A solution of musizin (3 g.) in ether was treated with excess of diazomethane in ether at 0°, and the solution was allowed to warm to room temperature during 1 hr. before being evaporated to dryness. The red syrup obtained, which crystallised on cooling, was extracted with light petroleum (b. p. 40—60°) (3 × 60 ml.) leaving a colourless residue (0·52 g.). Evaporation of the combined petroleum extracts gave red crystals (2·65 g.)

[12] W. B. Whalley, unpublished work.
[13] Miyasita, *J. Pharm. Soc. Japan*, 1940, **60**, 506.
[14] Eliel, Burgstahler, Rivard, and Haefele, *J. Amer. Chem. Soc.*, 1955, **77**, 5092.

XUM

which were purified by filtration first of an ether solution and then of a light-petroleum solution through alumina. The eluted solid was recrystallised from aqueous methanol to give needles of 1-O-*methylmusizin* (0·93 g.), m. p. 73—74° (Found: C, 72·7; H, 6·2; OMe, 12·9. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1; OMe, 13·5%); infrared bands in chloroform at 3360 and 1694 cm.$^{-1}$. The recrystallisation mother liquors yielded more monomethyl ether (0·66 g.), m. p. 65—70°. The solid, insoluble in light petroleum, was purified by chromatography of an ether solution on alumina and recrystallisation from aqueous methanol, giving needles of 8-O-*methylmusizin* (0·42 g.), m. p. 109—110° (Found: C, 72·8; H, 6·1; OMe, 13·3%); infrared bands in chloroform at 3360 and 1686 cm.$^{-1}$. Neither compound gave a colour with ferric chloride, but each dissolved in aqueous sodium hydroxide to give a yellow solution.

Demethylation and Methylation of the Monomethyl Ethers of Musizin.—8-*O*-Methylmusizin (0·2 g.) and pyridinium chloride (0·7 g.) were heated at 200—210° for 15 min. The dark green melt was digested with water, and the green precipitate recrystallised from light petroleum to give greenish-yellow needles of musizin (0·12 g.), m. p. 162—164°. Similar treatment of 1-*O*-methylmusizin also afforded musizin, m. p. 162—164°, in the same yield.

A mixture of 1-*O*-methylmusizin (0·11 g.), potassium carbonate (1 g.), acetone (10 ml.), and dimethyl sulphate (0·3 ml.) was boiled for 2 hr. The filtered solution was evaporated and treated with aqueous ammonia. The residual syrup, isolated with ether, was dissolved in benzene and filtered through a column of alumina. The eluted syrup crystallised from light petroleum in prisms of musizin dimethyl ether (0·09 g.), m. p. 76—78° undepressed by an authentic sample. Similar methylation of 8-*O*-methylmusizin also gave musizin dimethyl ether, m. p. 80—83°, in quantitative yield. The infrared spectrum of the product obtained was in each case identical with that of musizin dimethyl ether.

Acetates of the Monomethyl Ethers of Musizin.—1-*O*-Methylmusizin (0·2 g.), sodium acetate (0·5 g.), and acetic anhydride (7·5 ml.) were boiled under reflux for 18 hr. and then poured into water. The solid obtained was collected in ether and recrystallised from light petroleum, giving prisms of 8-O-*acetyl*-1-O-*methylmusizin* (0·14 g.), m. p. 97—98° (Found: C, 71·0; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). Under the same conditions 8-*O*-methylmusizin (0·2 g.) gave 1-O-*acetyl*-8-O-*methylmusizin* (0·15 g.) (from light petroleum), m. p. 110—111° depressed to 80—83° by starting compound (Found: C, 70·9; H, 5·9%).

8-*O*-Methylmusizin (0·11 g.), fused sodium acetate (0·25 g.), and acetic anhydride (2 ml.) were heated at 190° in a sealed tube for 5 hr. The mixture was then decomposed by water, and the product was extracted into ether. The evaporated solution gave a syrup which was dissolved in light petroleum. The filtered petroleum solution was evaporated and the partially crystalline mass crystallised from methanol, forming pale yellow needles of the *naphthopyrone* (II; R = Me) (0·016 g.), m. p. 172—174° (Found: C, 72·8; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%); $\lambda_{max.}$ in ethanol 242, 317, 364 mμ (log ε 4·64, 3·80, 3·94), $\lambda_{infl.}$ 214—220, 234—238, 262—268, 352—355 mμ (log ε 4·44, 4·62, 4·40, 3·91). The mother liquors from the methanol recrystallisation were evaporated to a syrup which was leached with hot light petroleum. On cooling of the petroleum solutions, 1-*O*-acetyl-8-*O*-methylmusizin (0·023 g.), m. p. 105—107°, crystallised. Recrystallisation gave material, m. p. 110—111° undepressed by an authentic sample.

Treatment of 1-*O*-methylmusizin (0·20 g.) under these conditions gave only 8-*O*-acetyl-1-*O*-methylmusizin (0·134 g.), m. p. 93—96° (raised to 97—98° by recrystallisation).

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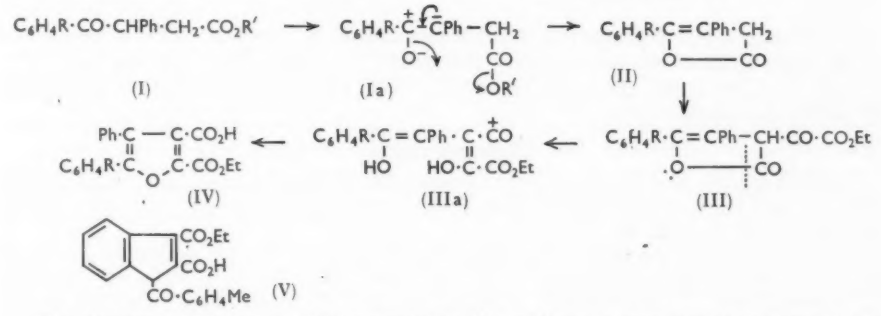
141. β-*Aroylpropionic Acids. Part XVIII.* Their Conversion into 4,5-Diarylfuran-2,3-dicarboxylic Acids.*

By F. G. Baddar and Sayed Sherif.

Ethyl β-phenyl-β-*p*-toluoyl- and -β-*p*-chlorobenzoyl-propionate, with ethyl oxalate in presence of potassium ethoxide, give 2-ethoxalyl-4-hydroxy-3-phenyl-4-*p*-tolyl- and -*p*-chlorophenyl-but-3-enoic acid lactone, respectively. These are cyclised with sulphuric acid to the corresponding 5-aryl-2-ethoxycarbonyl-4-phenylfuran-3-carboxylic acids.

Ethyl β-phenyl-β-*p*-toluoylpropionate (I; R = *p*-Me, R′ = Et) with ethyl oxalate and potassium ethoxide [1] gave 2-ethoxalyl-3-phenyl-4-*p*-tolylbut-3-enoic acid lactone (III; R = *p*-Me). Its structure was established by the following facts: (i) The same product was obtained when the ethyl ester (I; R′ = Et) was replaced by the methyl ester (I; R′ = Me) or by 3-phenyl-γ-4-tolylbut-3-enoic acid lactone [2] (II; R = *p*-Me). This indicates that the alkoxide ion $R'O^-$ is eliminated in the reaction. (ii) β-Aroyl-α- or β-arylpropionic esters are converted into the 2,4- or 3,4-diarylbut-3-enoic acid lactones through the intermediate carbanion (Ia), when treated with potassium ethoxide. (iii) The infrared spectrum showed stretching frequencies at 1640, 1755, and 1785 cm.$^{-1}$, characteristic of enolic carbonyl groups,[3a] α-keto-esters,[3b] and βγ-unsaturated lactones,[3b] respectively.

Warm 80% sulphuric acid converted the lactone (III; R = *p*-Me) into 2-ethoxycarbonyl-4-phenyl-5-*p*-tolylfuran-3-carboxylic acid (IV; R = *p*-Me). The reaction appears to proceed by intermediate formation of the carbonium ion (III*a*), as indicated by the green colour of the reaction mixture which disappeared at the end of the reaction. This colour is not given by the furan (IV) in 80% sulphuric acid.



The structure (IV; R = *p*-Me) assigned to the product is more probable than (V) for the following reasons: (i) The product decolorised alkaline potassium permanganate, a reaction which is given by furancarboxylic acids. (ii) On fusion with potassium hydroxide at 250—260°, it gives only the dibasic acid. However, at 290—300°, it was partially cleaved to give *p*-toluic acid. The failure to trace the presence of indene-2,3-dicarboxylic acid in the fusion product excluded structure (V), since indene-2,3-dicarboxylic acid is recovered unchanged when fused with alkali at 290—300°. (iii) It failed to respond to all ketonic reagents. (iv) Its infrared spectrum showed two bands, at 1760 and 1680 cm.$^{-1}$; the former is characteristic of the carboxylate group,[3b] the slight shift to shorter wavelength being perhaps due to conjugation of the carboxylate group with the electronegative carboxyl group.[3b] The band at 1680 cm.$^{-1}$ is undoubtedly due to the carboxyl

* Part XVII, *J.*, 1960, 3420.

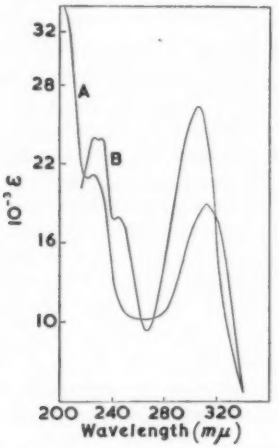
[1] Baddar and Warren, *J.*, 1939, 944; Baddar, Fleifel, and Sherif, *J.*, 1959, 1009.

[2] Baddar and Sherif, *J.*, 1960, 2309.

[3] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1956, pp. (*a*) 114, (*b*) 153, (*c*) 140, (*d*) 84, (*e*) 31, (*f*) 34.

XUM

group [3c] and not to a carbonyl group,[3a] since it was absent from the spectrum of the corresponding diethyl ester (see p. 709). (v) The ultraviolet spectrum (Figure) was similar to that of methyl 3,4,5-triphenylfuran-2-carboxylate (sample kindly provided by Professor G. Soliman, Faculty of Science, Alexandria University). (vi) The infrared spectra of the furan (IV) and of methyl 3,4,5-triphenylfuran-2-carboxylate include a weak band at 1620 and 1613 cm.$^{-1}$, respectively, characteristic of a conjugated double bond; [3e] their low intensities may be due to symmetry considerations.[3f]



Absorption spectra of (A) 2-*ethoxycarbonyl*-4-*phenyl*-5-p-*tolylfuran*-3-*carboxylic acid and* (B) *methyl* 3,4,5-*triphenylfuran*-2-*carboxylate.*

When ethyl β-*p*-chlorobenzoyl-β-phenylpropionate (I; R = *p*-Cl, R′ = Et) was subjected to the same series of reactions, it gave the lactone (III; R = *p*-Cl) and the furan (IV; R = *p*-Cl). The latter gave *p*-chlorobenzoic acid when refluxed with 10% aqueous potassium hydroxide.

Experimental

Infrared spectra were measured with a Perkin–Elmer Infracord spectrophotometer model 137, for Nujol mulls, and ultraviolet spectra with a Zeiss spectrophotometer model PMQ II, for EtOH or MeOH solutions.

Ethyl and *methyl* β-*phenyl*-β-p-*toluoylpropionate* were obtained from β-phenyl-β-*p*-toluoylpropionic acid [4] in the usual manner. The ethyl ester (90%) had b. p. 197—198°/0·6 mm., n_D^{20} 1·5581 (Found: C, 76·9; H, 6·5. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). The methyl ester had m. p. 109—110° [from benzene–light petroleum (b. p. 50—70°)] (Found: C, 76·5; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

2-*Ethoxalyl*-3-*phenyl*-4-p-*tolylbut*-3-*enoic Acid Lactone*.—(i) Finely powdered potassium (1·9 g., 1 g.-equiv.) was covered with dry ether (100 ml.), allowed to react with ethanol (3·5 ml.), then treated with freshly distilled ethyl oxalate (7·3 g., 1 mol.), followed by ethyl β-phenyl-β-*p*-toluoylpropionate (14·8 g., 1 mol.). The mixture was left overnight, then refluxed for 6 hr. and worked up.[1] The yellow crystals (10 g.) left on the removal of ether crystallised from benzene–light petroleum (b. p. 50—70°) to give 2-*ethoxalyl*-3-*phenyl*-γ-4-*tolylbut*-3-*enoic acid lactone*, m. p. 134—135° (Found: C, 71·6; H, 5·2. $C_{21}H_{18}O_5$ requires C, 72·0; H, 5·2%). It gave a deep-red colour with concentrated sulphuric acid, and a green colour with ferric chloride solution. Its infrared spectrum showed absorption bands at 1640, 1755, and 1785 cm.$^{-1}$. (ii) The same compound was obtained in inferior yields when the reaction was carried out with methyl β-phenyl-β-*p*-toluoylpropionate or 3-phenyl-4-*p*-tolylbut-3-enoic acid lactone [2] instead of the ethyl ester.

2-*Ethoxycarbonyl*-4-*phenyl*-5-p-*tolylfuran*-3-*carboxylic Acid*.—The above ethoxalyl ester (4 g.) was stirred with 80% (v/v) sulphuric acid (50 ml.) for 1 hr. at 50—60°, then for 2 hr. at

[4] Baddar, Fleifel, and Sherif, *Egypt. J. Chem.*, in the press.

room temperature. The red solution changed gradually to green but the solution was colourless at the end of the reaction. The mixture was poured into cold water, filtered off, and dried (3·5 g.). On crystallisation from benzene–light petroleum (b. p. 50—70°) it gave *2-ethoxycarbonyl-4-phenyl-5-p-tolylfuran-3-carboxylic acid*, m. p. 165—166° (Found: C, 71·95; H, 5·1. $C_{21}H_{18}O_5$ requires C, 72·0; H, 5·2%). It discharged the colour of alkaline potassium permanganate and gave a yellow colour with 80% (v/v) sulphuric acid. Its infrared spectrum showed bands at 1760 and 1680 cm.$^{-1}$.

Attempted cyclisation with concentrated sulphuric acid at 0—5° caused complete sulphonation.

4-Phenyl-5-p-tolylfuran-2,3-dicarboxylic Acid.—The above ester (1 g.) was refluxed for 1 hr. with 10% aqueous potassium hydroxide (50 ml.), then worked up as usual. *4-Phenyl-5-p-tolylfuran-2,3-dicarboxylic acid* (0·8 g.) had m. p. 230° (decomp.) (from xylene). It contains one molecule of water of crystallisation as shown by its infrared spectrum [3d] (sharp band at 3595 cm.$^{-1}$) and by analysis (Found: C, 67·0; H, 4·5. $C_{19}H_{14}O_5,H_2O$ requires C, 67·05; H, 4·75%). This water was removed at 140°/0·6 mm. in 2 hr. [Found: C, 71·0; H, 4·5%; *M* (Rast), 313; equiv., 160. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·4%; *M* (dibasic), 322]. The band at 3595 cm.$^{-1}$ had disappeared. Attempts to obtain an anhydride were unsuccessful: furan-2,3-dicarboxylic acid also fails to give an anhydride.[5] The *diethyl ester* was obtained by refluxing the monoethyl ester with absolute ethanol and concentrated sulphuric acid for 6 hr. and had m. p. 87—88° [from light petroleum (b. p. 50—70°)] (Found: C, 73·4; H, 5·8. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·9%), $\nu_{max.}$ 1745 and 1730 cm.$^{-1}$, characteristic of two carboxylate groups.[3b]

Action of Potassium Hydroxide on 2-Ethoxycarbonyl-4-phenyl-5-p-tolylfuran-3-carboxylic Acid and 4-Phenyl-5-p-tolylfuran-2,3-dicarboxylic Acid.—The ester or acid was fused with potassium hydroxide at 290—300° for 1 hr., and the mixture was worked up as usual to give *p*-toluic acid, identified by m. p. and mixed m. p. 181°. At 250—260° no cleavage took place.

Ethyl β-p-*Chlorobenzoyl-β-phenylpropionate.*—This *ester*, obtained (90%) from the corresponding acid,[2] had b. p. 205—207°/5 mm. (Found: C, 68·0; H, 5·3; Cl, 11·3. $C_{18}H_{17}ClO_3$ requires C, 68·2; H, 5·4; Cl, 11·2%).

2-Ethoxalyl-3-phenyl-4-p-chlorophenylbut-3-enoic Acid Lactone.—The preceding ester was converted in the usual manner into the yellow lactone (40%), m. p. 135—136° [from benzene–light petroleum (b. p. 50—70°)] (Found: C, 64·6; H, 4·1; Cl, 9·7; OEt, 10·8. $C_{20}H_{15}ClO_5$ requires C, 64·8; H, 4·1; Cl, 9·6; OEt, 12·1%), $\nu_{max.}$ 1645, 1740, and 1760 cm.$^{-1}$, giving a deep-red colour with alcoholic ferric chloride solution, and a red colour with concentrated sulphuric acid.

2-Ethoxycarbonyl-5-p-chlorophenyl-4-phenylfuran-3-carboxylic Acid.—The chloro-ester (as I) (3 g.) was stirred in 85% (v/v) sulphuric acid (60 ml.) at 60—65° for 2 hr., left overnight, and worked up as usual. The product (2·5 g.) crystallised from benzene, to give *5-p-chlorophenyl-2-ethoxycarbonyl-4-phenylfuran-3-carboxylic acid*, m. p. 192—193° (Found: C, 64·2; H, 4·0; Cl, 9·6. $C_{20}H_{15}ClO_5$ requires C, 64·8; H, 4·1; Cl, 9·6%). This discharged the colour of alkaline potassium permanganate, gave a yellow colour with concentrated sulphuric acid, and with refluxing 10% aqueous potassium hydroxide (1 hr.) gave *p*-chlorobenzoic acid, m. p. and mixed m. p. 239°.

3-p-Chlorophenyl-2-p-methoxyphenylbut-3-enoic Acid Lactone.—(i) A mixture of ethyl β-*p*-chlorobenzoyl-α-*p*-methoxyphenylpropionate,[2] potassium ethoxide [from potassium (1 g.) and absolute ethanol (2 ml.)], and ether (30 ml.) was left overnight, then refluxed for 5 hr. and worked up as usual.[1] The product was extracted with light petroleum (b. p. 50—70°) to remove unchanged ester, then with dilute sodium carbonate solution to remove traces of the acid. The insoluble residue crystallised from ethanol, to give *3-p-chlorophenyl-2-p-methoxyphenylbut-3-enoic acid lactone*, m. p. and mixed m. p.[2] 140—141°. (ii) A solution of β-*p*-chlorobenzoyl-α-*p*-methoxyphenylpropionic acid [2] (1 g.) in acetic anhydride (10 ml.) was refluxed for 3 hr., cooled, and poured into water. The lactone was filtered off and washed with dilute sodium carbonate solution. On crystallisation from ethanol, it was obtained, in quantitative yield, with m. p. and mixed m. p. 140—141°.

We thank the National Research Centre (Biochemistry Unit) for giving us the facilities to use their Zeiss spectrophotometer.

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[*Received, May* 31*st*, 1960.]

[5] Paul, *Bull. Soc. chim. France*, 1941, **8**, 369.

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142. *The Oxidation of Cyclic Phosphites to Cyclic Phosphates.*

By L. Keay and E. M. Crook.

The occurrence and synthesis of cyclic phosphates and the factors influencing ring formation, ring size, and stability are discussed with special reference to the degree of lability of the esters. Present methods for synthesis and their limitations are assessed. Ethyl esters of cyclic phosphates with five- and six-membered rings were prepared by the oxidation of the corresponding phosphites with mercuric oxide or dinitrogen tetroxide. The cyclic phosphates were also prepared by oxidation of cyclic phosphorochloridites and hydrolysis without isolation of the intermediate phosphorochloridate.

It has long been known that a neighbouring hydroxyl group renders phosphate esters more susceptible to alkaline hydrolysis [1] and leads to migration of the phosphate group in acid or alkaline conditions,[1-5] reaction proceeding through a cyclic phosphate.[2] The hydrolysis of ribonucleic acid and of pyrimidine nucleotide 3′-benzyl or -methyl ester by alkali or bovine pancreatic ribonuclease also proceeds through a cyclic phosphate [3,4] which has been isolated by Markham and Smith.[5] In these reactions five-membered rings are formed. Study of the cyclization of phosphate esters by Khorana and his colleagues [6] strongly suggests that this is the preferred form and is always formed if the stereochemical conditions permit; indeed these workers propose that the reaction has structural diagnostic implications. Nevertheless, larger rings can be made [6] and once formed resist hydrolysis to some extent by acid or alkali, the stability increasing rapidly with the ring size.[6-11] The stability of seven-membered ring compounds approaches that of simple dialkyl phosphates which have been shown to be hydrolysed 10^6 times more slowly than the five-membered ring compounds in alkaline solution.[12] The relative stabilities are very similar in acid solution and the recent preparation of adenosine 3′,5′-phosphate, which was shown to be fairly stable in both acid and alkali,[9,10] indicates that these findings must be of fairly general applicability.

The greater stability of six-membered than of five-membered rings to hydrolysis with acid was quantitatively confirmed during the course of the present work: the latter were hydrolysed at least 10^4 faster than the former in 0·05M-solution by 0·05N-hydrochloric acid.

Most syntheses of cyclic phosphates depend upon the availability of phosphate mono- or di-esters or pyrophosphate esters. Both five- and six-membered rings may be formed from diesters $-CH(OH)\cdot CH[O\cdot PO(OH)\cdot OR]-$ under alkaline conditions.[4,5,13,14] Five-membered rings may also be made by this reaction under acid conditions; *e.g.*, uridine 2′(3′)-(benzyl hydrogen phosphate) can be converted into uridine 2′,3′-phosphate in

[1] Bailly and Gaume, *Bull. Soc. chim. France*, 1936, **3**, 1396; Baer and Kates, *J. Biol. Chem.*, 1948, **175**, 79; 1950, **185**, 615; Leloir, *Arch. Biochem. Biophys.*, 1951, **33**, 186; Chargaff, *J. Biol. Chem.*, 1942, **145**, 455.

[2] Brown and Todd in " The Nucleic Acids," ed. Chargaff and Davidson, Academic Press, New York, Vol. I, 1955, p. 414.

[3] Brown and Todd, *J.*, 1952, 52.

[4] Brown, Dekker, and Todd, *J.*, 1952, 2715.

[5] Markham and Smith, *Biochem. J.*, 1952, **52**, 552.

[6] Khorana, Tener, Wright, and Moffat, *J. Amer. Chem. Soc.*, 1957, **79**, 430.

[7] Baddiley and Thain, *J.*, 1952, 3783.

[8] Bailly, *Bull. Soc. chim. France*, 1922, **31**, 848.

[9] Cook, Lipkin, and Markham, *J. Amer. Chem. Soc.*, 1957, **79**, 3607.

[10] Rall and Sutherland, *J. Biol. Chem.*, 1958, **232**, 1077.

[11] Rall and Sutherland, *J. Amer. Chem. Soc.*, 1957, **79**, 3608; Baddiley, Buchanan, and Szabó, *J.*, 1954, 3826.

[12] Kumamoto, Cox, and Westheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 4858.

[13] Lipkin and Talbert, *Chem. and Ind.*, 1955, 143.

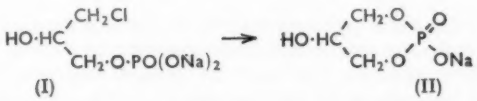
[14] Baddiley and Thain, *J.*, 1953, 903.

XUM

anhydrous trifluoroacetic acid.[6] Similarly, pyrophosphate diesters undergo ring closure

under alkaline conditions; *e.g.*, pantothenic acid 2′,4′-phosphate is obtained from coenzyme A,[9] and glucose 1,2-phosphate from uridine diphosphate glucose.[15] These methods usually give poor yields even under carefully controlled conditions and the starting materials are rarely readily accessible.

If the starting materials are the monoesters, some type of cyclising reagent must be used, although it is possible to esterify the phosphate group with the adjacent hydroxyl group in small yields by use of anhydrous trifluoroacetic acid.[16] The earliest method [8] of effecting cyclization was by the use of a halogenoalkyl phosphate, *e.g.*, (I) ⟶ (II), but this route [17] has the disadvantages of poor yields, difficulty in obtaining the halogenoalkyl phosphate, and possible inversion of configuration. More useful reagents include trifluoroacetic acid,[18] tetraphenyl pyrophosphate,[19] carbodi-imides,[6,20] and ethyl chloroformate,[21] and Crook *et al.*[16] have recorded valuable modifications. Ring sizes up to seven have been formed thus,[8] although five-membered rings are always formed if there is a free adjacent hydroxyl group in the correct steric orientation even when other hydroxyl groups are free.



(I) (II)

In the absence of suitable phosphate monoesters it has been possible to synthesise certain cyclic phosphates directly. For instance Baddiley and his colleagues used phosphoryl chloride in moist pyridine to form the cyclic phosphate of pantetheine,[14] and prepared methyl α-D-glucoside 4,6-phosphate by the use of phenyl phosphorodichloridate in pyridine with subsequent hydrogenation.[11] These do not appear to be general methods, however, and the yields are poor and the products difficult to purify.

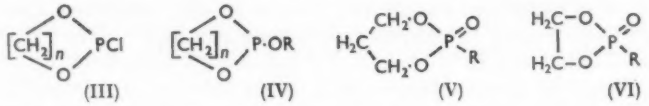
In considering alternative routes from unphosphorylated starting materials we noted that cyclic phosphorochloridites (III) and cyclic phosphite esters (IV) can readily be prepared in good yield,[22-24] and studied their conversion into cyclic phosphates. In agreement with previous experience,[23] attempts to form cyclic phosphorochloridates by treating the cyclic phosphite esters with halogens caused ring fission and gave halogenoalkyl phosphorochloridates. However, cyclic phosphites reacted vigorously with sulphur, to form cyclic thiophosphate esters, although the cyclic phosphorochloridites failed to react with sulphur.[12,25] These results suggested an investigation of the oxidation of cyclic phosphites to phosphates as a general synthesis. A wide range of oxidising agents had previously been used to oxidise phosphines, phosphites, and phosphonites to phosphine oxides, phosphates, and phosphonates respectively,[26] but aqueous solutions, especially acidic or alkaline ones, rapidly cleave many cyclic phosphates. Preliminary experiments

[15] Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426.
[16] Crook, Mathias, and Rabin, *Biochem. J.*, 1960, **74**, 230.
[17] Atherton, Openshaw, and Todd, *J.*, 1945, 382; Lecocq, *Compt. rend.*, 1956, **242**, 1902; cf. refs. 8 and 12.
[18] Brown, McGrath, and Todd, *J.*, 1952, 2708; Ukita, Bates, and Carter, *J. Biol. Chem.*, 1955, **216**, 867.
[19] Forrest, Mann, and Todd, *J.*, 1952, 2530.
[20] Moffat and Khorana, *J. Amer. Chem. Soc.*, 1957, **79**, 1194.
[21] Michelson, *J.*, 1959, 3655.
[22] Arbusov and Zorostrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1948, 208.
[23] Rossuiskaya and Kabachnick, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1947, 509.
[24] Lucas, Mitchell, and Scully, *J. Amer. Chem. Soc.*, 1950, **72**, 5491
[25] Yamasaki and Sato, *Sci. Reports Tôhoku Univ.*, 1954, **6**, *A*, 384; 1956, **8**, *A*, 45.
[26] Kosolapoff, " Organophosphorus Compounds," John Wiley & Co., New York, 1950.

XUM

were therefore carried out with yellow mercuric oxide to oxidise non-cyclic phosphites in acetone: triethyl, tri-isopropyl, and triphenyl phosphate were readily obtained in high yields.

The same simple procedure was used to prepare ethyl trimethylene phosphate and ethyl ethylene phosphate (V and VI; R = OEt), the yield of the latter being lower. The boiling points of these cyclic phosphates are much higher than those of similar open chain phosphates (ethyl trimethylene phosphate, b. p. 114—115°/0·1 mm.; triethyl phosphate, b. p. 106—108°/24 mm.) and the possibility of pyrophosphate formation was suspected. Infrared spectroscopy [27] showed that the cyclic phosphate possessed the



(III) (IV) (V) (VI)

strong absorption of the phosphoryl group at 1290 cm.$^{-1}$ and did not exhibit the P–O–P absorption at 870—970 or the hydroxyl absorption at 3400—3600 cm.$^{-1}$. Further, on mild hydrolysis with barium hydroxide, barium ethyl 3-hydroxypropyl phosphate was isolated; this could only arise from the cyclic phosphate or a symmetrical *PP'*-diethyl *PP'*-di-(3-hydroxypropyl)pyrophosphate, the latter being excluded by the spectroscopic evidence.

When yellow mercuric oxide was added to diethyl phosphite in acetone there was no apparent reaction as indicated by the lack of temperature and colour changes.

Recently, dinitrogen tetroxide was used to prepare aromatic aldehydes [28] and to oxidise sulphides and phosphines to their oxides.[29] We found dinitrogen tetroxide to oxidise triethyl phosphite to the phosphate in a slightly higher yield than did yellow mercuric oxide and to involve an even simpler procedure. Dinitrogen tetroxide in chloroform is green at low temperature and can be used as a self-indicating system. The reaction with trialkylphosphites is vigorous and external cooling is required. This method also gave ethyl ethylene and trimethylene phosphate in yields higher than did mercuric oxide. By both methods, the yield of the compound with the five-membered is somewhat lower than of that with the six-membered ring. Phenyl trimethylene phosphate [30] was also prepared by this method.

Because the cyclic phosphate group is more labile than other ester linkages hydrolysis of the cyclic triester cannot be considered a general synthesis of the cyclic hydrogen phosphates (V and VI; R = OH), and the oxidation of phosphorochloridites to phosphorochloridates was examined. Diethyl phosphorochloridate was obtained by using dinitrogen tetroxide; but when cyclic phosphorochloridites were oxidised, decomposition accompanied distillation at reduced pressure and only viscous polymers were obtained. As the oxidation appeared to have proceeded normally, immediate hydrolysis of the unisolated cyclic phosphorochloridates (V and VI; R = Cl) to the cyclic hydrogen phosphates (R = OH) was attempted. The main difficulty was to separate the product from the hydrochloric acid produced during hydrolysis. The solution had to be neutralised immediately to prevent hydrolysis of the cyclic phosphate, and the salts fractionated. Trimethylene hydrogen phosphate was best isolated as the guanidinium salt; dimethylene hydrogen phosphate was isolated as the silver salt and then converted into the guanidinium salt.

During this work, Cox and Westheimer [31] described the use of dinitrogen tetroxide for conversion of triphosphites and cyclic phosphorochloridites into the corresponding

[27] Corbridge, *J. Appl. Chem.*, 1956, 456; McIvor, Grant, and Hubley, *Canad. J. Chem.*, 1956, **34**, 1611.
[28] Field and Grundy, *J.*, 1955, 1110.
[29] Addison and Sheldon, *J.*, 1956, 2705.
[30] Ayres and Rydon, *J.*, 1957, 1109.
[31] Cox, jun., and Westheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5441.

triphosphates and cyclic phosphorochloridates. However, their yields were low and they were not able to hydrolyse the cyclic phosphorochloridate to the corresponding cyclic phosphate without opening the ring.

Experimental

Materials.—Acetone ("AnalaR") was dried with phosphoric anhydride and distilled. Chloroform was dried ($CaCl_2$) and distilled over anhydrous magnesium sulphate.

Dinitrogen tetroxide was prepared by Partington and Park's method.[32] Diethyl phosphorochloridite was prepared by the reaction of two equiv. each of ethanol and diethylaniline with one of phosphorous trichloride in ether at 0°; after filtration, the product was isolated by distillation (b. p. 54—56°/25 mm.). Ethylene phosphorochloridite, b. p. 48°/20 mm., trimethylene phosphorochloridite, b. p. 68—69°/19 mm., ethyl ethylene phosphite, b. p. 57—58°/19 mm., and ethyl trimethylene phosphite, b. p. 68—69°/16 mm., were prepared by the method of Lucas, Mitchell, and Scully.[24] Phenyl trimethylene phosphite, prepared from trimethylene phosphorochloridite and phenol in the presence of diethylaniline in ether at 0°, had b. p. 81—82°/0·3 mm. Other organophosphorus compounds used were available commercially.

Oxidation of Triethyl Phosphite.—(a) *With mercuric oxide.* To triethyl phosphite (16·6 g.), dissolved in anhydrous acetone (75 ml.), yellow mercuric oxide (35 g.) was added in small portions. The reaction is exothermic and external cooling was used. After several hours at room temperature, the mixture was filtered and evaporated, and the residual oil distilled, to yield triethyl phosphate (15·5 g., 85%), b. p. 106—108°/24 mm. (lit., b. p. 103°/25 mm.) (Found: C, 39·9; H, 8·3; P, 16·7. Calc. for $C_6H_{15}O_4P$: C, 39·6; H, 8·2; P, 17·0%). In similar experiments tri-isopropyl phosphite gave an 81% yield of tri-isopropyl phosphate, b. p. 100—102°/18 mm. (lit., b. p. 95°/10 mm.) (Found: C, 48·6; H, 9·1; P, 14·1. Calc. for $C_9H_{21}O_4P$: C, 48·2; H, 9·4; P, 13·8%), and triphenyl phosphite a 61% yield of triphenyl phosphate, m. p. 49—50° (lit., 50°) (from ethanol) (Found: C, 65·6; H, 4·5; P, 9·8. Calc. for $C_{18}H_{15}O_4P$: C, 66·3; H, 4·6; P, 9·5%).

(b) *With dinitrogen tetroxide.* To triethyl phosphite (16·6 g.) in dry chloroform (50 c.c.), cooled in acetone–solid carbon dioxide, a cooled solution of dinitrogen tetroxide in dry chloroform was added in small portions, with stirring and cooling, until a permanent green colour remained. After 1 hr. at room temperature, the solvent was removed at the water-pump and the residual oil distilled, to yield triethyl phosphate (15·7 g., 85%), b. p. 98—99°/19 mm. (lit., 103°/25 mm.) (Found: C, 39·5; H, 8·0; P, 17·2%).

Oxidation of Diethyl Phosphorochloridite with Dinitrogen Tetroxide.—Diethyl phosphorochloridite (15·6 g.) in chloroform (50 ml.) was oxidized as described above, to yield on distillation diethyl phosphorochloridate (10·1 g., 58%), b. p. 94—96°/18 mm. (lit., b. p. 93—95°/18 mm.) (Found: C, 27·5; H, 5·9; P, 18·3; Cl, 20·2. Calc. for $C_4H_{10}ClO_3P$: C, 27·8; H, 5·8; P, 18·0; Cl, 20·6%).

Oxidation of Ethyl Ethylene Phosphite.—(a) *With mercuric oxide.* Ethyl ethylene phosphite (27·2 g.) in acetone (100 ml.) was oxidized by addition of mercuric oxide (75 g.) in small portions with cooling. After attaining room temperature overnight, the mixture was filtered, the solvent removed at the water-pump, and the residual oil distilled *in vacuo*, to yield *ethyl ethylene phosphate* (8·5 g., 28%), b. p. 106—108°/0·7—0·8 mm. (Found: C, 32·2; H, 6·4; P, 20·0. $C_4H_9O_4P$ requires C, 31·6; H, 5·9; P, 20·4%).

(b) *With dinitrogen tetroxide.* To ethyl ethylene phosphite (15·0 g.) in dry chloroform (50 ml.), cooled in ice, a solution of dinitrogen tetroxide was added, dropwise, with stirring until a permanent green colour remained. After 0·5 hr. the solvent was removed and the residual oil distilled, to yield ethyl ethylene phosphate (7·0 g., 42%), b. p. 89—90°/0·3 mm. (Found: C, 32·1; H, 6·1; P, 20·5%).

Oxidation of Ethyl Trimethylene Phosphite.—(a) *With mercuric oxide.* To ethyl trimethylene phosphite (15·0 g.) in anhydrous acetone (100 ml.), mercuric oxide was added in small portions with cooling and shaking until no further reaction occurred. The solids were removed by

[32] Partington and Park, *J.*, 1924, **125**, 74.

XUM

centrifugation and the solvent was evaporated from the supernatant liquid. The residual oil was distilled, to yield *ethyl trimethylene phosphate* (8·7 g., 52%), b. p. 114—115°/0·1 mm. (Found: C, 35·6; H, 6·7; P, 18·8. $C_5H_{11}O_4P$ requires C, 36·2; H, 6·6; P, 18·7%).

(b) *With dinitrogen tetroxide.* To ethyl trimethylene phosphite (18·0 g.) in anhydrous chloroform (100 ml.), cooled to −20° in acetone–solid carbon dioxide, dinitrogen tetroxide in chloroform was added dropwise with shaking until a faint permanent green colour remained. After 0·5 hr. at −20°, the mixture was allowed to warm to room temperature during 1 hr. and then evaporated at water-pump pressure. Distillation of the residual oil yielded ethyl trimethylene phosphate (12·8 g., 65%), b. p. 114—116°/0·1 mm. (Found: C, 36·0; H, 6·8; P, 18·3%).

Oxidation of Phenyl Trimethylene Phosphite.—Phenyl trimethylene phosphite (10 g.) was oxidized with dinitrogen tetroxide as described in the previous section. Removal of the solvent yielded a brown oil. The oil was redissolved in chloroform (50 ml.) and shaken with three portions of activated alumina and filtered. Carbon tetrachloride was added and the solution partially evaporated. On cooling, needles (8·2 g., 76%) of phenyl trimethylene phosphate were obtained; they had m. p. 74—75° (lit., m. p. 76—77°) alone or mixed with a sample provided by Professor H. N. Rydon (Found: C, 50·0; H, 5·1; P, 15·2. Calc. for $C_9H_{11}O_4P$: C, 50·5; H, 5·1; P, 14·5%).

Hydrolysis of Ethyl Trimethylene Phosphate.—Ethyl trimethylene phosphate (0·7 g.) was heated at 80° for 10 min. with barium hydroxide octahydrate (0·5 g.) in water (5 ml.); ethanol (5 ml.) was added and the mixture filtered. Acetone (100 ml.) was added with shaking. The precipitate was filtered off, washed with acetone, and dried, to yield *barium ethyl 3-hydroxypropyl phosphate* (0·4 g.) (Found: C, 23·1; H, 5·1; P, 12·1. $C_{10}H_{24}BaO_{10}P_2$ requires C, 23·8; H, 4·8; P, 12·3%).

Preparation of Guanidinium Trimethylene Phosphate.—Trimethylene phosphorochloridite (7·0 g.) in anhydrous chloroform was oxidized with dinitrogen tetroxide as described above. The chloroform was removed under reduced pressure and the residual oil poured into cold water and neutralized with a solution of guanidine carbonate. After being stirred for 1 hr., the solution was brought to pH 7·0 with guanidine carbonate solution. Acetone was added until a permanent turbidity was formed. A colorless oil separated at 0°, but when shaken with more acetone, slowly crystallized, to give *guanidinium trimethylene phosphate* (5·0 g., 52%) (Found: C, 24·2; H, 6·8; N, 20·6; P, 15·7. $C_4H_{12}N_3O_4P$ requires C, 24·4; H, 6·1; N, 21·2; P, 15·7%). Titration showed that no dissociation occurred between pH 4 and 10, *i.e.*, there is no secondary phosphate dissociation.

Preparation of Silver Ethylene Phosphate.—Ethylene phosphorochloridite (6·3 g.) in chloroform was oxidized as above with dinitrogen tetroxide and the solvent removed under reduced pressure. The residual oil was poured into cold water and shaken and a suspension of silver acetate (16·7 g.) in water added. After 1 hour's stirring, the pH was raised to 7·0 by the addition of triethylamine, and the silver chloride was filtered off, the filtrate freeze-dried, and the solid dissolved in hot water (500 ml.), cooled and filtered. The volume was reduced and the solution again filtered off. Finally, the filtrate was freeze-dried, to give *silver ethylene phosphate* (4·0 g., 43%) (Found: C, 10·1; H, 2·1; P, 13·0; Ag, 46·3. $C_2H_4AgO_4P$ requires C, 10·4; H, 1·7; P, 13·4; Ag, 46·7%).

Conversion of Silver Ethylene Phosphate into the Guanidinium Salt.—Silver ethylene phosphate (2·3 g.) in water was added to a solution of guanidine hydrochloride (0·95 g.), and the silver chloride filtered off. The filtrate was freeze-dried, the residual white powder dissolved in boiling methanol, and an excess of anhydrous ether added. At −10°, white crystals were obtained; these were filtered off and washed with ether, to give *guanidinium ethylene phosphate* (1·73 g., 88%) (Found: C, 19·9; H, 5·8; N, 22·2; P, 16·5. $C_3H_{10}N_3O_4P$ requires C, 19·7; H, 5·4; N, 22·9; P, 16·9%). Titration showed that there was no dissociation between pH 4 and 8.

Hydrolysis of Guanidinium Ethylene and Trimethylene Phosphate.—0·1M-Cyclic phosphate solution (5·0 ml.) was mixed with 0·1M-hydrochloric acid (5·0 ml.). An aliquot part was removed immediately and the pH adjusted to 4·5 by the addition of 0·05N-sodium hydroxide, a pH meter being used. The secondary phosphate dissociation present was then estimated by measuring the further volume of sodium hydroxide required to bring the pH to 9·0. The remainder of the solution was then placed in a constant-temperature bath, and further aliquot parts were removed at suitable time intervals and titrated in the same way. The appearance

of secondary phosphate dissociation is expressed in the Table as the percentage hydrolysis of the cyclic phosphate.

	Guanidinium ethylene phosphate						Guanidinium trimethylene phosphate			
Min. at 37°	0	5	15	25	360	Hr. at 100°	0	2	5	24
Hydrolysis (%)...	0	27	48	63	100	Hydrolysis (%) ...	0	5	10	25

Paper Chromatography.—Ascending chromatography (see Table) was carried out on Whatman No. 1 paper with 50% v/v propan-2-ol–water as the developing system. Phosphate esters were detected by the method of Hanes and Isherwood,[33] and guanidine by the α-naphthol–biacetyl method.[34] Some samples were incubated with a suspension of *Crotalus adamanteus* venom before chromatography, as this venom is known to hydrolyse phosphate diesters and would therefore indicate the nature of the compound under test.

R_P values.

	Phosphate reagent	Guanidine reagent
Silver ethylene phosphate	0·80	—
Guanidinium ethylene phosphate	0·77	0·78
Venom-treated guanidinium ethylene phosphate	0·60	—
Acid-treated guanidinium ethylene phosphate	0·59	
Guanidinium trimethylene phosphate	0·71	0·71
Venom-treated guanidinium trimethylene phosphate	0·52	—
Acid-treated guanidinium trimethylene phosphate	0·71, 0·51	—

We thank Professor H. N. Rydon for a sample of phenyl trimethylene phosphate, the Research Department, Albright and Wilson's, for measuring the infrared spectra, and Professor J. M. Buchanan and Dr. A. P. Mathias for advice in preparing this manuscript. One of us (L. K.) thanks the Salters' Institute of Industrial Chemistry for the award of a Research Fellowship (1956—1958).

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[*Received, August 3rd,* 1960.]

[33] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.
[34] Smith, "Chromatographic Techniques," Interscience Publ. Inc., New York, 1958, p. 154.

143. *Studies on Phosphorylation. Part XXII.* Phosphorylation accompanying the Oxidation of Quinol Phosphates.*

By V. M. Clark, D. W. Hutchinson, G. W. Kirby, and Sir Alexander Todd.

Oxidation of several quinol phosphates by a variety of oxidising agents has been studied. Evidence is presented for the production of a phosphorylating agent during the oxidation.

The methods used for studying phosphorylation *in vitro* have been closely related to those leading to anhydride formation followed by acylation.[1] As phosphorylating agents, phosphoric anhydrides, *e.g.*, phosphorochloridates [2] and pyrophosphates,[3] have often been used, phosphorylation then proceeding with the expulsion of an anion:

$$\text{Base} + \text{ROH} + (\text{R'O})_2\text{POCl} \longrightarrow \text{RO·PO(OR')}_2 + \text{Base, HCl}$$

$$(\text{RO})_2\text{PO·O}^- + (\text{R'O})_2\text{POCl} \longrightarrow (\text{RO})_2\text{PO·O·PO(OR')}_2 + \text{Cl}^-$$

$$2(\text{RO})_2\text{PO·O}^- + (\text{R'O})_2\text{PO·O·PO(OR')}_2 \longrightarrow (\text{RO})_2\text{PO·O·PO(OR)}_2 + 2(\text{R'O})_2\text{PO'·O}^-$$

* Part XXI, *J.*, 1960, 4511.

[1] Todd, *Gazzetta*, 1959, **89**, 126; *Proc. Nat. Acad. Sci.*, 1959, **45**, 1389.
[2] Brigl and Müller, *Ber.*, 1939, **72**, 2121; Atherton, Openshaw, and Todd, *J.*, 1945, 382.
[3] Corby, Kenner, and Todd, *J.*, 1952, 1234.

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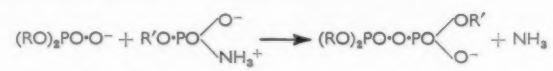
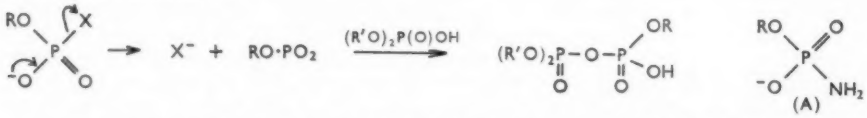
The phosphoramidates require to be in the zwitterionic form to exhibit their acylating function, the expelled group then being a neutral amine molecule:

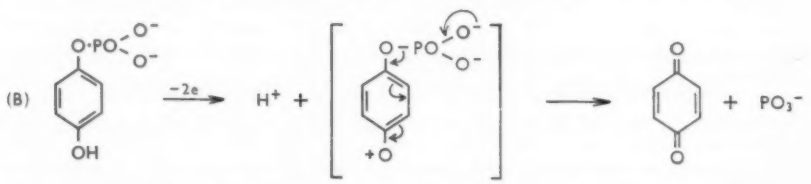


By this method, adenosine diphosphate has been converted into the triphosphate in high yield [4] and coenzyme A has been synthesised.[5] In this type of reaction, the expulsion of the amine molecule may precede rather than accompany acylation; the intermediate would then be a monomeric metaphosphate which would rapidly phosphorylate an appropriate substrate: [6]



In such reactions the heterolysis of the phosphorus–nitrogen bond giving the metaphosphate [7] follows the withdrawal of electrons from the P–N bond as the new N–H bond is being formed during the protonation of the anion (A). The metaphosphate is to be regarded as a hypothetical intermediate, since no monomeric metaphosphate has yet been described, although trimers are well known.[8] The phosphoramidates can be described as metaphosphates which have been converted into complexes or solvates by amines, the esters of phosphoric acid as products from metaphosphates and alcohols, and the pyrophosphates as the products of interaction of metaphosphates and orthophosphates.

The heterolysis of the P–N bond in the phosphoramidates can, in theory, be accomplished by removing electrons with an oxidising agent rather than with a proton. The facility of the acid cleavage of the phosphoramidates has, however, precluded their being studied under a wide range of oxidising conditions and attention has been turned to other systems, particularly those in which a phosphorus atom is combined solely with oxygen atoms. In the case of a quinol monophosphate, the scheme (B) can be envisaged:



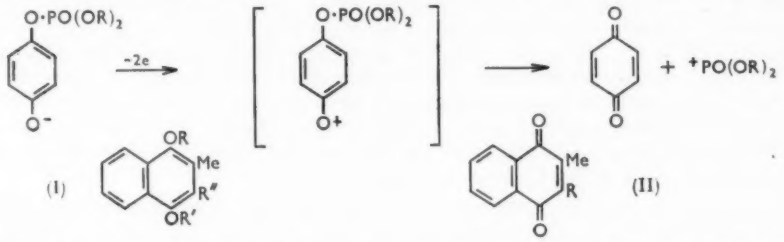
The expected oxidation and concomitant phosphorylation have been substantiated experimentally. Thus, whereas diphenyl 4-hydroxy-2,3-dimethyl-1-naphthyl phosphate is relatively stable to oxidising agents (unchanged by bromine in methanol after 10 minutes at room temperature), the monoesters and the free hydroxynaphthyl dihydrogen phosphate undergo immediate oxidation with bromine to the quinone and various products derived from metaphosphate, *viz.*, trimetaphosphate, pyrophosphate, and orthophosphate. These observations imply that a metaphosphate is easily produced, but not the phosphoryl cation.

4-Hydroxy-3-methyl-1-naphthyl dihydrogen phosphate [I; R = H, R′ = $PO(OH)_2$, R″ = H] in aqueous solution at pH 6·8 in the presence of air is slowly hydrolysed with

[4] Clark, Kirby, and Todd, *J.*, 1957, 1497.
[5] Khorana and Moffatt, *J. Amer. Chem. Soc.*, 1959, **81**, 1265.
[6] Vernon, *Chem. Soc. Spec. Publ.*, 1957, **8**, 23; Bunton, Llewellyn, Oldham, and Vernon, *J.*, 1958, 3574.
[7] Cf. Goehring and Sambeth, *Chem. Ber.*, 1957, **90**, 232.
[8] Van Wazer, "Phosphorus and its Compounds," Interscience Publ. Inc., New York, 1958, Vol. I, Chap. 11.

the liberation of inorganic phosphate (half-life ~4 days); in air-free solution there is no appreciable decomposition for 1 week. In alkaline solution rapid autoxidation greatly complicates further investigation.

The corresponding bisphosphate ("Synkavit") [I; $R = R' = PO(OH)_2$, $R'' = H$] is very stable to hydrolysis; after 6 hr. at 80° (pH 5) only about 20% of the phosphorus



appears as inorganic phosphate (personal communication from Dr. K. J. M. Andrews, Roche Products, Ltd.). On treatment in aqueous solution with a variety of oxidising agents, however, rapid decomposition ensues. Ceric sulphate in 3N-sulphuric acid brings about immediate oxidation to the quinone (II; R = H), so does bromine in aqueous solution, one mol. of halogen being used without incorporation into the aromatic nucleus. As the bisphosphate is very resistant to hydrolysis, the dephosphorylation must accompany and not precede the oxidation. Metabolic studies of this bisphosphate, carried out in view of its potent inhibition of mitosis of cultures of chick-heart fibroblasts [9] and its radiosensitising action,[10] have indicated a rapid dephosphorylation *in vivo* [11] and this, too could be oxidative in type. It is noteworthy that the oxidation of dihydrovitamin K_3 (I; $R = R' = R'' = H$) by mitochondria is accompanied by phosphorylation,[12] and a rôle associated with phosphorylative reactions has been suggested for vitamin K in studies on animal tissue,[13] bacteria,[14] and chloroplasts.[15]

Oxidation of the bisphosphate to the corresponding quinone by bromine can be carried out in aqueous solution over a wide pH range, the metaphosphate intermediate being solvated to orthophosphate. Notwithstanding the water present, this oxidation in the presence of orthophosphate leads to formation of some inorganic pyrophosphate concurrently with precipitation of the quinone; that is, orthophosphate is phosphorylated to pyrophosphate in consequence of an oxidation. Moreover, in the absence of added orthophosphate, 10% of inorganic pyrophosphate was formed; and on oxidation in dry *NN*-dimethylformamide 35% of the phosphorus was transformed into trimetaphosphate and 15% of pyrophosphate was produced. These observations are most readily accommodated by considering the, as yet unknown, monomeric metaphosphate to have been generated in these reactions. Finally, oxidation in glacial acetic acid gave rise to the anhydride, acetyl phosphate, whose formation was detected by the formation of acethydroxamic acid on treatment with hydroxylamine.

A variety of quinol diphosphates have been oxidised by bromine water to quinones (see Table, p 719). For a variety of oxidising agents, qualitative correlation between their efficacy and the redox potential of the quinol–quinone system was noted. In almost all cases, oxidation by ceric ion or bromine was rapid. Derivatives of catechol required the substitution of chlorine for bromine before they would undergo oxidative dephosphorylation with the production of pyrophosphate. 4-Hydroxy-3-methyl-1-naphthyl

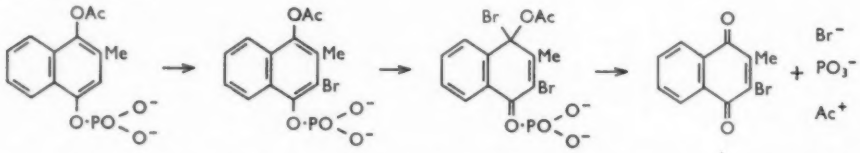
[9] Mitchell and Simon-Reuss, *Nature*, 1947, **160**, 98.
[10] Mitchell, *Brit. J. Cancer*, 1952, **6**, 305.
[11] Neukomm, Peguiron, Lerch, and Richard, *Arch. Int. Pharmacodyn. Therapie*, 1953, **93**, 373.
[12] Colpa-Boonstra and Slater, *Biochim. Biophys. Acta*, 1958, **27**, 122.
[13] Martius, *Biochem. Z.*, 1956, **327**, 407.
[14] Brodie and Ballantine, *J. Biol. Chem.*, 1960, **235**, 226.
[15] Arnon, Allen, and Whatley, *Biochim. Biophys. Acta*, 1956, **20**, 449.

XUM

phosphate was only slowly oxidised by acid dichromate, hydrogen peroxide in the presence of tungstate,[16] or dilute nitric acid; neither iodine not potassium ferricyanide produced any apparent change within an hour at room temperature.

Certain other acyl derivatives of dihydrovitamin K_3 (I; R = R′ = R″ = H) undergo oxidation to the quinone. Ceric sulphate rapidly oxidises the disulphate [17] (I; R = R′ = SO_2·OH, R″ = H), presumably to the quinone, whilst bromine in aqueous solution reacts with both the acetate phosphate [I; R = Ac, R′ = $PO(OH)_2$, R″ = H] and the monoacetate (I; R = Ac, R′ = R″ = H) to give 2-bromo-3-methyl-1,4-naphthaquinone (II; R = Br). This nuclear bromination is in contrast to the behaviour of the bisphosphate and 2-methyl-1,4-naphthaquinol (I; R = R′ = R″ = H), both of which give the halogen-free quinone (II; R = H). Since the diacetate (I; R = R′ = Ac, R″ = H) is unaffected by bromine in aqueous dioxan, the phosphorylated phenolic groups appear to be polarisable, and in this sense still phenolic.

Bromination of the acetate phosphate probably takes the following course, oxidation being accompanied by a phosphorylation (by PO_3^-) and an acetylation (by CH_3·CO^+ or its equivalent).



Esters of quinol monophosphates are now readily available from the reaction between a quinone and a diester of phosphorous acid. Ramirez and Dershowitz [18] described the reaction following photochemical activation, but we have found the same products are formed extremely smoothly in the presence of small quantities of base, *e.g.*, potassium t-butoxide. The reaction appears to be general. 2,3-Dimethylnaphthaquinone and dibenzyl phosphite give dibenzyl 4-hydroxy-2,3-dimethyl 1-naphthyl phosphate, and this with lithium chloride [19] in ethyl cellosolve affords the monobenzyl ester, which with bromine gave some P^1P^2-dibenzyl pyrophosphate; the same oxidative phosphorylation has been achieved by hydrogen transfer to another quinone, chloranil.

Experimental

Oxidation of 4-Hydroxy-3-methyl-1-naphthyl Phosphate.—4-Acetoxy-3-methyl-1-naphthyl phosphate [20] (100 mg.; dried at 100°/0·1 mm. over P_2O_5) was dissolved in 0·1N-sodium hydroxide solution (5 ml.) with exclusion of air and left at room temperature for 1½ hr. The reaction vessel was opened and the solution quickly adjusted to pH 7 with 3N-hydrochloric acid and examined chromatographically in butan-1-ol–acetic acid–water (5 : 2 : 3) (see below). The chromatogram showed that removal of the acetyl group was complete and that a little inorganic orthophosphate had been produced, presumably by autoxidation, since the solution had become slightly discoloured by the end of the reaction. 0·1N-Iodine solution (5 ml.; containing potassium iodide) was added to this solution of 4-hydroxy-3-methyl-1-naphthyl phosphate; 2-methyl-1,4-naphthaquinone that was immediately precipitated was collected, washed, dried, and recrystallised from light petroleum (b. p. 60—80°) (20 mg.; m. p. and mixed m. p. 103—106°). Titration of the excess of iodine in the filtrate with sodium thiosulphate solution showed that 0·87 mol. of iodine had been consumed. The original acetoxy-phosphate was not affected by iodine under these conditions.

In another experiment an aqueous solution of the naphthaquinol monophosphate at pH 6·8

[16] Cf. Spencer, Todd, and Webb, *J.*, 1958, 2968.
[17] Canbäck and Ehrlen, *Farmacevtisk Revy* (*Stockholm*), 1947, **12**, 210.
[18] Ramirez and Dershowitz, *J. Org. Chem.*, 1957, **22**, 1282.
[19] Clark and Todd, *J.*, 1950, 2030.
[20] Baker and Carlson, *J. Amer. Chem. Soc.*, 1942, **64**, 2657; Baker, U.S.P. 2,380,716, *Chem. Abs.*, 1945, **39**, 4727.

(prepared as described above) was divided into two portions, one of which was sealed under a vacuum. The other portion was kept open to the atmosphere at room temperature and examined chromatographically from time to time. After 4 days some 50% of the quinol phosphate had been hydrolysed to orthophosphate, the solution having become deep red. After 7 days the sealed specimen was unchanged.

Oxidation of Various Quinol Phosphates with Bromine.—The quinol diphosphates (supplied by Roche Products, Ltd., and prepared as directed by Andrews *et al.*[21]) and 4-acetoxy-3-methyl-1-naphthyl phosphate were used as their hydrated normal sodium salts. The degree of hydration of these salts was determined by drying at 100°/0·1 mm. over P_2O_5.

Method (*a*). A solution of the sodium salt (500 mg.) in water (5 ml.) was treated at room temperature with a freshly prepared, saturated aqueous solution of bromine. The oxidising agent was added slowly with stirring until a slight excess was present. In all cases, the quinone began to separate almost immediately. Each suspension was cooled to 0° and then filtered, and the quinone washed with water, dried, and recrystallised from light petroleum (b. p. 60—80°).

Method (*b*). The procedure differed from (a) in that sodium acetate (1 g. of the trihydrate) was dissolved in the aqueous quinol phosphate solution before bromine was added. Under these conditions the pH of the solution did not fall below 7 during the reaction.

The results are tabulated. The yields quoted are of purified material; in some cases the yield of crude product was appreciably greater.

Substrate	Method	Product isolated	Yield (%)
2,3-Dimethyl-1,4-naphthaquinol bisphosphate	a	2,3-Dimethyl-1,4-naphthaquinone	62
2-Methyl-1,4-naphthaquinol bisphosphate	a	2-Methyl-1,4-naphthaquinone *	63
1,4-Naphthaquinol bisphosphate †	a	1,4-Naphthaquinone	53
4-Acetoxy-3-methyl-1-naphthyl phosphate	a	2-Bromo-3-methyl-1,4-naphthaquinone	31
Duroquinol bisphosphate	a	Duroquinone	53
	b		54
2,3,5-Trimethylquinol bisphosphate	a	2-Bromo-3,5,6-trimethyl-1,4-benzoquinone	10
	b		70
2-Bromo-3,5,6-trimethylquinol bisphosphate	a	2-Bromo-3,5,6-trimethyl-1,4-benzoquinone	42
	b		51
2,5-Dimethylquinol bisphosphate	a	A mixture of quinones, m. p. 80—100°	10 ‡
	b		15 ‡

* This product melted at 101—103°, even after recrystallisation from light petroleum or ethanol. Authentic 2-methyl-1,4-naphthaquinone melted at 106°, and the infrared spectrum of our product suggested the presence of a small amount of 2-bromo-3-methyl-1,4-naphthaquinone (extra bands at 1280, 1180, 822, and 700 cm.$^{-1}$). † The normal barium salt was used. ‡ Calc. as 3-bromo-2,5-dimethyl-1,4-benzoquinone.

Oxidations of 4-Hydroxy-3-methyl-1-naphthyl Bisphosphate.—(a) *With* Ce^{4+}.[22] To a solution of the tetrasodium salt of this phosphate (500 mg. of the hexahydrate) in N-sulphuric acid (10 ml.) was added 0·1N-ceric sulphate (20 ml.; N with respect to sulphuric acid). The 2-methyl-1,4-naphthaquinone that was precipitated was filtered off, washed with N-sulphuric acid and water, dried, and recrystallised from light petroleum (b. p. 60—80°); it had m. p. 105—106° (100 mg., 62%). The combined filtrate and washings were treated with an excess of potassium iodide, and the liberated iodine was titrated with thiosulphate (Ce consumed, 2·02 equiv.).

(b) *With bromine.* The tetrasodium salt (250 mg.) was oxidised with saturated aqueous bromine (5 ml.) as described above. The precipitated quinone was filtered off and washed, the filtrate and washings were run into an excess of aqueous potassium iodide, and the liberated iodine was titrated with thiosulphate. The bromine content of the aqueous bromine solution was determined separately (Br consumed, 1·03 mol.).

(c) *With other oxidising agents.* An aqueous solution of the tetrasodium salt was stable towards iodine and ferricyanide, but was slowly oxidised by dichromate in 3N-sulphuric acid and by hydrogen peroxide solution containing sodium pertungstate. Oxidation by this last

[21] Andrews, Marrian, and Maxwell, *J.*, 1956, 1844.
[22] Yamagishi, *Ann. Reports Takeda Res. Lab.*, 1954, **13**, 25.

XUM

reagent gave a crystalline precipitate of 2-methyl-1,4-naphthaquinone 2,3-oxide,[23] m. p. and mixed m. p. 95—97° (from aqueous ethanol).

Irradiation of an aqueous solution of the tetrasodium salt with ultraviolet light (Hg discharge lamp) in the absence of air brought no hydrolysis.

Formation of Pyrophosphate and Trimetaphosphate in the Oxidation of 4-*Hydroxy*-3-*methyl*-1-*naphthyl Bisphosphate.*—(a) *In aqueous solution.* To a solution of the tetrasodium salt (20 mg. of the hexahydrate) in water (0·25 ml.) one drop of bromine was added. The mixture was left at room temperature for 10 min. and the excess of bromine and precipitated quinone were removed by extraction with cyclohexene (2·5 ml.). The aqueous phase was examined by paper chromatography, with trichloroacetic acid–propan-2-ol–water–ammonia (see below) as solvent. Pyrophosphate was present, together with orthophosphate. The relevant spots were cut out and, together with controls from a developed chromatogram containing no phosphorus, were eluted with water and analysed for phosphorus.[24] The oxidation produced 90% of orthophosphate and 10% of pyrophosphate.

(b) *In non-aqueous solution.* The tetrasodium salt was converted into the free acid by passing its aqueous solution through Dowex-50 (H^+ form) resin. The eluate was concentrated *in vacuo* and the crystalline residue dried (P_2O_5). To a solution of this free acid (35 mg.) in rigorously dried [25] *NN*-dimethylformamide (1 ml.) bromine (0·1 ml.) was added and the mixture left at room temperature for 1 hr. Water (10 ml.) was added, followed by cyclohexene (5 ml.), and the aqueous layer was examined by paper chromatography with the above solvent system. Three phosphorus-containing spots were observed, at R_P 0·66, 0·35, and 0·10, corresponding to ortho-, pyro-, and trimeta-phosphate, respectively. Excision, elution, and estimation, as in the previous experiment, indicated that 50% of orthophosphate, 15% of pyrophosphate, and 35% of trimetaphosphate had been produced.

Oxidation of o-*Hydroxyphenyl Phosphate with Chlorine.*—Chlorine was passed into a solution of cyclohexylammonium *o*-hydroxyphenyl hydrogen phosphate [26] in dry *NN*-dimethylformamide for 15 min. The solution became pale brown and heat was evolved. Paper chromatography with butanol–acetic acid–water (see below) revealed inorganic pyrophosphate. Repetition of the oxidation in the presence of tetra-n-butylammonium phosphate produced a large amount of inorganic pyrophosphate.

Formation of Acetyl Phosphate.—A slight excess of bromine was added to a solution of the tetrasodium 4-hydroxy-3-methyl-1-naphthyl bisphosphate in glacial acetic acid and, after 2 hr., the solution was diluted with water and the precipitated quinone extracted with ether. The presence of acetyl phosphate in the remaining aqueous layer was shown in the following way.[27] A portion of the solution was treated with hydroxylamine hydrochloride followed by aqueous sodium hydroxide and then examined chromatographically with butan-1-ol–acetic acid–water (5 : 2 : 3). A ferric chloride–hydrochloric acid spray revealed a substance (red colour) having the R_F value (0·57) of acethydroxamic acid. Repetition of the experiment using 1,4-naphthaquinol gave none of this product.

Oxidation of 2-*Methyl*-1,4-*naphthaquinol and its* 1-*Acetate with Bromine.*—To a solution of 4-hydroxy-2-methyl-1-naphthyl acetate (300 mg.) in dioxan (10 ml.) containing water (5 ml.) was added saturated aqueous bromine, with stirring, until a slight excess was present. The mixture was diluted with water to 50 ml. and kept at 0° for 30 min.; the precipitated 2-bromo-3-methyl-1,4-naphthaquinone was collected, dried (331 mg.), and recrystallised from light petroleum (b. p. 60—80°) (260 mg., 74%), then having m. p. and mixed m. p. 156—158°. 2-Methyl-1,4-naphthaquinol, when oxidised in analogous fashion, gave 2-methyl-1,4-naphthaquinone (56%), m. p. and mixed m. p. 105—107°.

Dibenzyl 4-*Hydroxy*-2,3-*dimethyl*-1-*naphthyl Phosphate.*—A 1·07N-solution (5 ml.) of potassium t-butoxide in t-butyl alcohol was added to one of 2,3-dimethyl-1,4-naphthaquinone (5 g., 0·03 mole) and dibenzyl phosphite (9·6 g., 0·035 mole) in dry benzene (25 ml.) and the mixture set aside overnight at room temperature in an atmosphere of nitrogen, moisture being excluded. The excess of benzene was then removed *in vacuo*. The residue crystallised on trituration with pentane. Recrystallised from carbon tetrachloride *dibenzyl* 4-*hydroxy*-2,3-*dimethyl*-1-*naphthyl*

[23] Weitz, Schobbert, and Siebert, *Ber.*, 1935, **68**, 1163.
[24] Allen, *Biochem. J.*, 1940, **34**, 858.
[25] Thomas and Rochow, *J. Amer. Chem. Soc.*, 1957, **79**, 1843.
[26] Cherbuliez, Schwarz, and Leber, *Helv. Chim. Acta*, 1951, **34**, 841.
[27] Cf. Stadtman and Barker, *J. Biol. Chem.*, 1950, **184**, 769.

phosphate formed needles (11 g., 82%), m. p. 110° (Found: C, 69·2; H, 5·1. $C_{26}H_{25}O_5P$ requires C, 69·5; H, 5·6%).

Benzyl 4-Hydroxy-2,3-dimethyl-1-naphthyl Hydrogen Phosphate.—The above dibenzyl ester (10·3 g.) was heated at 80° for 2 hr. in ethyl cellosolve (50 ml.) saturated with anhydrous lithium chloride.[19] 10% Aqueous sodium hydroxide (40 ml.) was added to the cooled solution, and the mixture extracted with ether (4 × 50 ml.). The aqueous layer was acidified and extracted with ether, and the extract washed, dried ($MgSO_4$), and evaporated. The residue recrystallised from chloroform, giving the *monobenzyl ester* as needles (5·96 g., 73%), m. p. 126—127° (Found: C, 63·9; H, 5·8. $C_{19}H_{19}O_5P$ requires C, 63·6; H, 5·3%).

Oxidation. (*a*) With bromine. To a solution of the monobenzyl ester (10 mg.) in dry *NN*-dimethylformamide (5 ml.) dry benzene (5 ml.) was added and then distilled off again *in vacuo* with strict exclusion of moisture. A drop of bromine was added to the solution and after 10 min. cyclohexene (1 ml.). Examination of the mixture by paper chromatography with propan-2-ol–water–ammonia (7 : 2 : 1) showed the presence of monobenzyl dihydrogen phosphate and P^1P^2-dibenzyl dihydrogen pyrophosphate.

(*b*) With chloranil. Chloranil (70 mg.) was added to a similarly prepared solution of the monobenzyl ester (70 mg.) in dry *NN*-dimethylformamide (5 ml.), and the mixture left for 1 hr. at room temperature. Paper chromatography showed the presence of monobenzyl dihydrogen phosphate and P^1P^2-dibenzyl dihydrogen pyrophosphate in the resulting solution.

4-Hydroxy-2,3-dimethyl-1-naphthyl Phosphate.—The above dibenzyl ester (3 g.) in absolute ethanol (30 ml.) was hydrogenated at room temperature and 1 atm. over palladium black (100 mg.). After uptake of hydrogen had ceased the catalyst was removed and the solvent evaporated under reduced pressure in a stream of nitrogen, to give *4-hydroxy-2,3-dimethyl-1-naphthyl dihydrogen phosphate* as hygroscopic needles; recrystallised from carbon tetrachloride, they (1·5 g., 85%) had m. p. 140° (Found: C, 52·4; H, 5·8. $C_{12}H_{13}O_5P,\frac{1}{2}H_2O$ requires C, 52·0; H, 5·1%). The crystals rapidly became pink in air.

Oxidation. To a solution of the free acid (72 mg.) in 0·05M-aqueous potassium carbonate (10 ml.) was added an excess of bromine water, and the mixture was set aside for 15 min. The precipitate was filtered off and dried overnight at 100°/0·1 mm. (42 mg., 96%); it had m. p. 123—124° undepressed in admixture with 2,3-dimethyl-1,4-naphthaquinone.

Oxidation under neutral or acidic conditions gave a virtually quantitative yield of 2,3-dimethyl-1,4-naphthaquinone in each case.

Diphenyl 4-Hydroxy-2,3-dimethyl-1-naphthyl Phosphate.—Prepared by the same method as the above dibenzyl compound, the *diphenyl ester* (yield, 65%) crystallised from ethyl acetate as hygroscopic needles, m. p. 94—95° (Found: C, 65·6; H, 5·4. $C_{24}H_{21}O_5P,H_2O$ requires C, 65·6; H, 5·4%).

The diphenyl ester was recovered unchanged (10 min.) in methanol solution with excess of bromine at room temperature.

Chromatographic Data.—Ascending chromatograms (see Table) were run on Whatman No. 1 paper in solvent systems (A) butan-1-ol–acetic acid–water (5 : 2 : 3) and (B) propan-2-ol (75 ml.)–water (25 ml.)–trichloroacetic acid (5 g.)–ammonia solution (0·25 ml.; *d* 0·88). Phosphorus was detected by the molybdate spray.

	R_F in solvent system A	R_F in solvent system B	Appearance of spot in u.v. light
2-Methyl-1,4-naphthaquinol bisphosphate	0·32	0·76	Blue fluorescence
4-Hydroxy-3-methyl-1-naphthyl phosphate	0·53	—	Blue fluorescence
4-Acetoxy-3-methyl-1-naphthyl phosphate	0·60	—	u.v. absorbing
Inorganic orthophosphate	0·30	0·66	—
Inorganic pyrophosphate	0·15	0·36	—
Inorganic trimetaphosphate	—	0·10	—

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XUM

144. *Studies on Phosphorylation. Part XXIII.* Oxidative Phosphorylation leading to Adenosine-5′ Pyrophosphate.*

By V. M. Clark, D. W. Hutchinson, and Sir Alexander Todd.

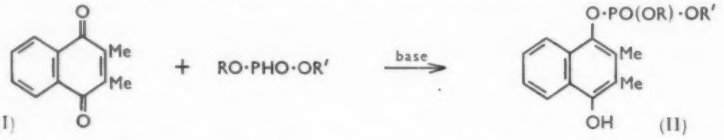
Oxidation of the monophosphate of a naphthaquinol in presence of a salt of adenosine-5′ phosphate or of a naphthaquinol ester of adenosine-5′ phosphate in presence of inorganic phosphate yields adenosine-5′ pyrophosphate (ADP).

The important rôle played by the coupling of substrate oxidation to the synthesis of adenosine-5′ triphosphate (ATP) in the functioning of animal cells is well known.[1] The demonstration *in vitro* of energetic coupling between the oxidation and reduction of carriers in the respiratory chain and ATP synthesis requires particulate preparations containing either mitochondria or multifunctional mitochondrial fragments. The detailed mechanism of this energetic coupling in the respiratory chain is essentially unknown and its elucidation constitutes a major problem of contemporary biochemistry. Recent evidence [2] suggests that benzoquinone derivatives [3] of the coenzyme Q type or naphthaquinone derivatives [4] related to vitamin K play an important part in phosphate transfer during oxidation–reduction processes.

In the preceding paper we reported the oxidation of a variety of phosphorylated quinols by a range of oxidising agents. In many of these reactions inorganic pyrophosphate was formed, and it was suggested that the effective acylating agent was related to the monomeric metaphosphate which, though as yet unknown, is assumed to be produced. Nucleophilic attack on the "metaphosphate" by orthophosphate can then produce the pyrophosphate.[5] Monoesters of quinol phosphoric acids should yield esters of "metaphosphate" which, in the presence of inorganic phosphate, should give rise to esters of pyrophosphoric acid.

Using reactions of this type, we have synthesised adenosine-5′ pyrophosphate by two routes, in one of which phosphate was transferred to adenosine-5′ phosphate as substrate, and in the other a naphthaquinol ester of adenosine-5′ phosphate was oxidised to transfer the nucleotide residue to added inorganic phosphate.

The esters of quinol monophosphates are now readily available by interaction of a quinone and a diester of phosphorous acid.[6,7] Reaction of 2,3-dimethyl-1,4-naphthaquinone with the nucleoside phosphite [8] (I; R = CH_2Ph, R′ = 2′,3′-*O*-isopropylideneadenosine-5′)



led, after anionic debenzylation by sodium thiocyanate,[9] to the naphthaquinol ester of the nucleotide (II; R = H, R′ = 2′,3′-O-isopropylideneadenosine-5′), and this was oxidised

* Part XXII, preceding paper.

[1] Lehninger, "Harvey Lectures," 1955, Series 39, p. 176.
[2] Green, D. E., "Quinones in Electron Transport," Ciba Foundation Symposium, Churchill, London, 1960, in the press.
[3] Wolf, Hoffman, Trenner, Arison, Shunk, Linn, McPherson, and Folkers, *J. Amer. Chem. Soc.*, 1958, **80**, 4752.
[4] Brodie and Ballantine, *J. Biol. Chem.*, 1960, **235**, 226.
[5] Cf. Vernon, *Chem. Soc. Spec. Publ.*, 1957, No. 8, p. 23.
[6] Ramirez and Dershowitz, *J. Org. Chem.*, 1957, **22**, 1282.
[7] Clark, Hutchinson, Kirby, and Todd, preceding paper.
[8] Corby, Kenner, and Todd, *J.*, 1952, 3669.
[9] Clark and Todd, *J.*, 1950, 2030; Morrison and Atherton, B.P. 675,779.

by bromine water to 2′,3′-*O*-isopropylideneadenosine-5′ phosphate and 2,3-dimethyl-1,4-naphthaquinone.

Bromine oxidation of 4-hydroxy-2,3-dimethyl-1-naphthyl phosphate (II; R = R′ = H) in dry *NN*-dimethylformamide in presence of the mono(tetrabutylammonium) salt of adenosine-5′ phosphate led to adenosine-5′ pyrophosphate, which was isolated as the barium salt and converted into the free acid. The quinone was extracted from the reaction mixture by addition of cyclohexene which also removed excess of bromine and the hydrogen bromide generated in the reaction. Omission of this step led to the breakdown of the adenosine pyrophosphate by the acid present. It was expected that adenosine triphosphate might also be formed in this reaction, but none was detected by paper chromatography or paper electrophoresis. However, the behaviour on ion-exchange chromatography did suggest that a small amount of higher polyphosphates was present.

In the second synthesis the 4-hydroxy-2,3-dimethyl-1-naphthyl ester of 2′,3′-*O*-isopropylideneadenosine-5′ phosphate was oxidised under the same conditions with bromine in the presence of added orthophosphate. Adenosine-5′ pyrophosphate was again produced and isolated from the reaction mixture as the free acid.

Experimental

Tetrabutylammonium Adenosine-5′ Phosphate.—Silver nitrate (1·05 g., 0·06 mole) in water (15 ml.) was added to a solution of adenosine-5′ phosphate (1·14 g. of dihydrate, 0·03 mole) in warm water (50 ml.), and the silver salt was then precipitated by addition of an equal volume of ethanol. The salt (1·25 g., 0·027 mole) was removed by centrifugation, washed with ethanol and ether, air-dried, and shaken for 18 hr. with tetrabutylammonium iodide (1·0 g., 0·027 mole) in 50% aqueous methanol (50 ml.). The precipitated silver iodide was filtered off and the solvent removed *in vacuo*. The *product* (1·2 g., 75%), recrystallised from ethanol–ethyl acetate, formed needles, m. p. 187° (Found: C, 51·5; H, 8·3; N, 14·1. $C_{26}H_{49}N_6O_7P,H_2O$ requires C, 51·5; H, 8·4; N, 13·9%).

Oxidation of 4-Hydroxy-2,3-dimethyl-1-naphthyl Phosphate in Presence of Adenosine-5′ Phosphate.—4-Hydroxy-2,3-dimethyl-1-naphthyl phosphate [7] (2·5 g., 0·0095 mole) and mono(tetrabutylammonium) adenosine-5′ phosphate monohydrate (1·8 g., 0·003 mole) were dissolved in anhydrous *NN*-dimethylformamide [10] (15 ml.), and benzene (15 ml.) was added. The benzene was removed *in vacuo* with exclusion of moisture. A further 10 ml. of anhydrous benzene were then added and removed *in vacuo* as before.

Bromine (0·7 ml., 0·0125 mole) was introduced and the mixture left at room temperature for 1 hr., after which cyclohexene (20 ml., 0·2 mole) was added and the mixture left at room temperature for a further 15 min. Solvents were removed under reduced pressure below 40° and the residue stirred with water. 2,3-Dimethyl-1,4-naphthaquinone was filtered off and the filtrate extracted with ether (2 × 25 ml.). The aqueous layer was shaken *in vacuo* to remove dissolved ether and washed on to an Amberlite IR-120 column (H^+ form; 2 cm. × 30 cm.). The column was washed with water until the washings had a negligible optical density at 260 mμ and the eluate and washings were then freeze-dried. The residual gum was dissolved in freshly distilled ethanol (5 ml.) and transferred to a 250 ml. centrifuge bottle with further small portions of ethanol (total, 15 ml.). Dry ether (200 ml.) at 0° was added and the solid centrifuged off. This solid was redissolved in ethanol (15 ml.) and the precipitation procedure repeated three times. The solid obtained was dissolved in a small volume of water and adjusted to pH 6 with sodium hydroxide solution. The solution of sodium salts was washed on to a Dowex-1 column (Cl^- form; 1·5 × 25 cm.), and the subsequent elution followed by measuring light absorption at 260 mμ, adenosine mono- and pyro-phosphate being assumed to have ε 14,200 at this wavelength.[11] Elution with 0·005N-hydrochloric acid gave 165 ml. of solution with an average optical density 3·3; this was unchanged adenosine-5′ phosphate (0·038 mmole, 1·3%). Elution with 0·01N-hydrochloric acid containing 0·1M-sodium chloride gave two fractions: the first (165 ml.; average optical density 16·0) contained adenosine-5′ phosphate (0·186 mmole, 6·3%); the second (1500 ml.; average optical density 4·81) contained adenosine-5′ pyrophosphate (0·52 mmole, 17%). Further elution with 0·01N-hydrochloric acid containing 0·20 ml. of

[10] Thomas and Rochow, *J. Amer. Chem. Soc.*, 1957, **79**, 1843.
[11] Chargaff and Davidson, "Nucleic Acids," Academic Press, New York, 1955, Vol. I, p. 513.

XUM

sodium chloride (1600 ml.; average optical density 1·7) and 0·1M-hydrochloric acid containing 0·2M-sodium chloride (900 ml.; average optical density 1·2) gave adenosine-5′ pyrophosphate (0·27 mole, 9%). From ultraviolet-absorption measurements the total yield of adenosine-5′ pyrophosphate was 26%.

The fractions containing adenosine-5′ pyrophosphate were adjusted to pH 6—7 with N-sodium hydroxide and evaporated to dryness, the last traces of water being removed by freeze-drying. The solid residue was dissolved in the minimum amount of water (5 ml.), and 20% w/v barium acetate solution (1·5 ml.) was added. Precipitation of solid was completed by addition of ethanol (10 ml.). The precipitate was centrifuged off and washed with water (1 ml.), 50% aqueous ethanol (2 × 20 ml.), absolute ethanol (20 ml.), and ether (20 ml.).

The product was dried *in vacuo* over phosphorus pentoxide (yield, 250 mg.); further crops of barium adenosine pyrophosphate were obtained by evaporating later fractions (yield, 350 mg., slightly contaminated with chloride). The barium salt was examined by paper electrophoresis at pH 4 and by chromatography in butanol–acetic acid–water and trichloroacetic acid–propan-2-ol–water–ammonia.[7] In each system the compound migrated as a single ultraviolet-absorbing, phosphorus-containing spot indistinguishable from authentic adenosine-5′ pyrophosphate.

The barium adenosine pyrophosphate was converted into the free acid by exact neutralisation with 0·1N-sulphuric acid. Barium sulphate was centrifuged off and the supernatant liquor brought to pH 7·5 with sodium hydroxide. A small amount of precipitate was removed by centrifugation and the supernatant liquor was poured on an Amberlite IR-120 column (H^+ form; 1 × 8 cm.). The column was washed with water until the washings had negligible optical density at 260 mμ; the washings were freeze-dried, giving adenosine-5′ pyrophosphate (60 mg., 84% based on Ba salt) (Found, in material dried over P_2O_5/0·1 mm.: C, 28·4; H, 4·1; N, 16·0; P, 14·1. Calc. for $C_{10}H_{15}N_5O_{10}P_2$: C, 28·1; H, 3·5; N, 16·3; P, 14·5%).

Enzymic assay using phospho-enol pyruvate–pyruvate kinase and myokinase showed the sample to have 83% of the activity of an authentic sample supplied by the Sigma Chemical Co., St. Louis.

Benzyl 4-Hydroxy-2,3-dimethyl-1-naphthyl 2′,3′-O-Isopropylideneadenosine-5′ Phosphate.—To a solution of benzyl 2′,3′-*O*-isopropylideneadenosine-5′ phosphite [8] (9·43 g., 0·02 mole) and 2,3-dimethyl-1,4-naphthaquinone in dry, thiophen-free benzene (50 ml.), potassium t-butoxide in t-butyl alcohol (7 ml. of 1·3N-solution) was added. The mixture was warmed at 40° for 30 min., then left at room temperature for 5 hr. Solvents were then removed *in vacuo* and the residue was dissolved in chloroform (200 ml.) and washed with an equal volume of water, then twice with an equal volume of 0·001N-hydrochloric acid, and again with water. The chloroform layer was dried ($MgSO_4$) and concentrated to small bulk. Pentane was added; the oil which separated crystallised on trituration (9·6 g.). The product was not further purified but was used immediately for the next stage of the synthesis.

4-Hydroxy-2,3-dimethyl-1-naphthyl 2′,3′-O-isopropylideneadenosine-5′ Hydrogen Phosphate.—The product from the previous experiment (3·97 g., 1 mol.) and anhydrous sodium thiocyanate (1·0 g., 2 mol.) were heated in ethyl methyl ketone (25 ml.) for 2 hr. and then left at room temperature overnight. Solvent was removed *in vacuo*, the residual sodium salt dissolved in warm water (200 ml.), insoluble matter centrifuged off, and the cloudy supernatant liquid acidified. The precipitated *4-hydroxy-2,3-dimethyl-1-naphthyl 2′,3′-O-isopropylideneadenosine-5′ hydrogen phosphate* was centrifuged off and dried over phosphoric oxide; it (yield, 1·05 g. 30%) had m. p. 64—65° (Found: C, 50·1; H, 5·4. $C_{25}H_{28}N_5O_8P,2H_2O$ requires C, 50·4; H, 5·4%).

Oxidation of 4-Hydroxy-2,3-dimethyl-1-naphthyl 2′,3′-O-Isopropylideneadenosine-5′ Hydrogen Phosphate.—(a) *In aqueous solution.* The product from the previous reaction (100 mg.) was dissolved in 0·1N-aqueous lithium hydroxide (5 ml.), and saturated bromine water was added to give pH 5. The quinone produced was removed in chloroform (3 × 10 ml.), and the aqueous layer was evaporated to dryness *in vacuo*. The residual solid was triturated with 5 : 1 acetone–ethanol and washed with acetone and pentane, to leave *2′,3′-O-isopropylideneadenosine-5′ dilithium phosphate* (30 mg., 45%) (Found: C, 34·4; H, 4·8. $C_{13}H_{16}Li_2N_5O_7P,3H_2O$ requires C, 34·2; H, 4·8%). The product ran as a single spot (R_F 0·54) in butan-1-ol–acetic acid–water (5 : 2 : 3) on Whatman No. 1 paper.

(b) *In presence of di(tetrabutylammonium) hydrogen phosphate in* NN-*dimethylformamide.* 4-Hydroxy-2,3-dimethyl-1-naphthyl 2′,3′-*O*-isopropylideneadenosine-5′ phosphate (500 mg., 1 mol.) and di(tetrabutylammonium) hydrogen phosphate (600 mg., 1 mol.) were dissolved in

dry *NN*-dimethylformamide (10 ml.), and dry benzene (10 ml.) was added and removed *in vacuo* with exclusion of moisture. A further 10 ml. of dry benzene were added and again removed *in vacuo*. Bromine (0·16 ml., 3 mol.) was next added and the mixture left at room temperature for an hour; cyclohexene (10 ml.) was introduced with shaking and the mixture left a further 15 min. Solvents were removed at $<40°/0·1$ mm., the residue stirred with water (10 ml.), and the aqueous solution extracted with ether (3 × 10 ml.). A precipitate was removed from the aqueous layer (120 mg.). This was soluble in alkali, gave a quinone on oxidation, and had R_F identical with that of the starting material in butanol–acetic acid–water and trichloroacetic acid–water–propan-2-ol–ammonia;[7] this represented 24% of unchanged starting material.

The filtrate was shaken *in vacuo* to remove ether and was then transferred to an Amberlite IR-120 column (H^+ form; 1·5 × 15 cm.). The column was washed until the washings had a negligible optical density at 260 mμ, and the washings were freeze-dried. Electrophoresis of the residue at pH 4 (2 v/cm.) for 14 hr. showed three products: orthophosphate, and two ultraviolet-absorbing and phosphorus-containing materials with the same mobilities as adenosine-5′ phosphate and adenosine-5′ pyrophosphate. This freeze-dried residue was dissolved in dry, freshly distilled ethanol (10 ml.) and transferred to a 250 ml. centrifuge bottle with a further 5 ml. of ethanol. Dry ether (200 ml.) at 0° was added and the precipitate centrifuged off, redissolved in ethanol, and precipitated with ether a further three times. The final precipitate was dissolved in water (10 ml.) and brought to pH 6 with N-sodium hydroxide, then applied to a Dowex-1 column (Cl^- form; 2 × 15 cm.), and the subsequent elution was followed by ultraviolet absorption at 260 mμ. The column was washed with water (giving little ultraviolet absorbing material), then with 0·005N-hydrochloric acid. The major fraction (600 ml.; average optical density 1·7) was adenosine-5′ phosphate (10%). 0·02N-Hydrochloric acid containing 0·25M-sodium chloride gave an eluate (600 ml.; average optical density 3·75) containing adenosine-5′ pyrophosphate (yield, 22%). Finally, with 0·1N-hydrochloric acid containing 0·4M-sodium chloride, a fraction (1 l.) containing no ultraviolet-absorbing material was obtained. The fraction containing the adenosine-5′ pyrophosphate was evaporated to dryness and the solid washed with water (5 × 1 ml.). 20% w/v Barium acetate (1 ml.) was added and then ethanol (5 ml.). The precipitate was centrifuged off and washed with water (1 ml.), 50% ethanol (2 × 25 ml.), absolute ethanol (25 ml.), and finally ether (25 ml.). This barium salt was dried *in vacuo* over phosphoric oxide (yield, 85 mg.; 80% recovery of ultraviolet-absorbing material). With the metaperiodate–Schiff reagent spray [12] it gave a purple colour showing the presence of a *cis*-glycol. Electrophoretic and chromatographic examination indicated that there was only one ultraviolet-absorbing, phosphorus-containing compound. This was indistinguishable from authentic adenosine-5′ pyrophosphate.

The barium salt (85 mg.) was shaken with Amberlite IR-120 (H^+ form; 5 ml.) and water (5 ml.) until it dissolved. The solution and resin were then washed on to an Amberlite IR-120 column (H^+ form; 1 × 5 cm.), and the column washed until the eluate had negligible optical density at 260 mμ. The eluate and washings were freeze-dried to yield adenosine-5′ pyrophosphate (45 mg.) (Found, in material dried over silica gel at 12 mm.: C, 26·7; H, 4·3; N, 15·9; P, 14·3. Calc. for $C_{10}H_{15}N_5O_{10}P_2,H_2O$: C, 27·0; H, 3·8; N, 15·7; P, 14·3%).

Enzymic assay using phospho-enol pyruvate–pyruvate kinase and myokinase showed the sample to have 85% of the activity of an authentic sample supplied by the Sigma Chemical Co., St. Louis.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance (to D. W. H.) and to Roche Products, Ltd., for the generous provision of certain materials. We are indebted to Dr. J. B. Chappell (Dept of Biochemistry, Cambridge) for enzymic assays.

University Chemical Laboratory,
Lensfield Road, Cambridge. [*Received, August 19th*, 1960.]

[12] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

XUM

145. *Kinetics of the Bromination of Ethyl Malonate and Methyl Methanetricarboxylate.*

By R. P. Bell and D. J. Rawlinson.

The rates of bromination of ethyl malonate and methyl methanetricarboxylate have been measured in aqueous solution, bromine concentrations in the range 10^{-5}—10^{-8}M being used. Under these conditions the rate is closely proportional to the bromine concentration, and approximate velocity constants are derived for the reaction of the enols and enolate ions with molecular bromine and tribromide ion.

The halogenation of many carbonyl compounds is believed to take place through the enol or the enolate ion, but since these reactions are usually of zero order with respect to the halogenating agent little is known about the velocity of the halogenation step. In principle this step must become rate-determining if the concentration of halogenating agent is reduced sufficiently, and Bell and Spiro [1] found that the rate of bromination of ethyl malonate became dependent on the bromine concentration in the range 10^{-2}—10^{-4}M. They were able to obtain approximate velocity constants for the bromination of the enol and the enolate ion, and similar information was obtained indirectly for the iodination of ethyl malonate [2] and 2-oxocyclohexanecarboxylate [3] by studying the reverse de-iodination reaction. Recently the measurement of redox potentials has been used to study the fast bromination reactions of anilines,[4] anisoles and phenols,[5] with bromine concentrations in the range 10^{-5}—10^{-8}M. The present paper describes similar measurements for the bromination of ethyl malonate and methyl methanetricarboxylate, special attention being paid to the relative reactivities of molecular bromine and tribromide ion. At these low concentrations the bromination step is almost completely rate-determining, and since only a very small proportion of the ester (<1%) is brominated it is not necessary to allow for the further bromination of ethyl monobromomalonate.

If the ester (RH) is present in large excess and is in equilibrium with very small proportions of the ion R^- and the enol HR, then the rate of disappearance of bromine is given by

$$-\mathrm{d}y/\mathrm{d}t = k_2[\mathrm{Br_2}][\mathrm{R^-}] + k_2'[\mathrm{Br_3^-}][\mathrm{R^-}] + k_3[\mathrm{Br_2}][\mathrm{HR}] + k_3'[\mathrm{Br_3^-}][\mathrm{HR}] \quad . \quad (1)$$

where y is the total bromine concentration $[\mathrm{Br_2}] + [\mathrm{Br_3^-}]$. If the ester concentration is c, the reaction velocity can be represented by a second-order constant $k = -\frac{1}{c}\frac{\mathrm{d}\ln y}{\mathrm{d}t}$, given by:

$$k(1 + K[\mathrm{Br^-}]) = k_2K_a/[\mathrm{H^+}] + k_2'KK_a[\mathrm{Br^-}]/[\mathrm{H^+}] + k_3K_E + k_3'KK_E[\mathrm{Br^-}] \quad (2)$$

where the equilibrium constants are $K = [\mathrm{Br_3^-}]/[\mathrm{Br_2}][\mathrm{Br^-}] = 16$, $K_a = [\mathrm{H^+}][\mathrm{R^-}]/[\mathrm{RH}]$, $K_E = [\mathrm{HR}]/[\mathrm{RH}]$. The constants k_2' and K_a should strictly contain ionic activity coefficients, but their values are not known with sufficient certainty to justify this. It has already been shown [4] that k is related to the change in e.m.f. at 25° by the equation

$$k = -\frac{1}{c}\frac{\mathrm{d}\ln y}{\mathrm{d}t} = -\frac{1}{c}\frac{\mathrm{d}\ln[\mathrm{Br_2}]}{\mathrm{d}t} = -\frac{78{\cdot}2}{c}\cdot\frac{\mathrm{d}E}{\mathrm{d}t} \quad . \quad . \quad . \quad (3)$$

so that the velocity constants k_2, k_2', k_3, and k_3' can in principle be derived from measurements at different acidities and concentrations of bromide ions.

[1] Bell and Spiro, *J.*, 1953, 429.
[2] Bell and Engel, *J.*, 1957, 247.
[3] Bell and Vogelsong, *J.*, 1958, 243.
[4] Bell and Ramsden, *J.*, 1958, 161.
[5] Bell and Rawlinson, *J.*, 1961, 63.

If the initial bromine concentration is not sufficiently low there will be departures from these simple kinetics in the early part of the reaction, and dE/dt will increase with time. We assume that there is always rapid equilibrium between the enol and its anion, but that the rate of formation of enol and anion from the ester is characterized by a first-order constant k_1 whose value depends on the catalysts present. The usual steady-state assumptions give

$$-dy/dt = kk_1yc/(ky + k_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

with y still defined by (2), which can be integrated to give

$$t + \frac{y}{k_1c} = -\frac{1}{kc} \ln y + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Comparing this with (3), we see that the plot of E against t should become linear if the times are corrected by adding y/k_1c: this was in fact the case for ethyl malonate. The values of y were derived from the observed potential, and k_1 from earlier measurements at high bromine concentrations.[1,6]

No correction of this kind was found necessary in the bromination of methyl methanetricarboxylate. Its rate of ionization has not been measured, but its relatively high acidity ($pK = 7{\cdot}86$) suggests $k_1 > 10$ sec.$^{-1}$, which would not have an appreciable effect on the observed rates of bromination. It was not practicable to work with the initial concentration of this ester greatly in excess of the initial bromine concentration, but after the latter had fallen by about one power of ten the concentration of ester remained effectively constant, and the plot of E against t was strictly linear for at least $0{\cdot}06V$ beyond this point. The value of c used in equation (3) was corrected for the ester removed in the early stages of the reaction.

Experimental

Ethyl malonate was repeatedly fractionated under reduced pressure until no further change was produced in the kinetic results. Methyl methanetricarboxylate, m. p. 43°, was prepared as described in "Organic Syntheses"[7] and dried over phosphoric oxide. Inorganic reagents were of "AnalaR" quality, and water was redistilled from potassium permanganate in a glass still.

Kinetic measurements were made by the method previously described.[4,5] The initial concentration of malonic ester was about 4×10^{-3}M in experiments with acetate buffers, and about 4×10^{-2}M in those with acid solutions: in each case the initial bromine concentration was about 4×10^{-5}M. In experiments with methyl methanetricarboxylate the initial ester concentration was about 2×10^{-5}M and that of bromine about 9×10^{-6}M. All measurements were at 25°.

The dissociation constant of methyl methanetricarboxylate was determined in 0·2M-sodium

Table 1. *Bromination of ethyl malonate.*

(*a*) Acetate buffer, $[HOAc] = [OAc^-] = 1{\cdot}99 \times 10^{-2}$

$[H^+] = 2{\cdot}93 \times 10^{-5}$, ionic strength made up to $I = 0{\cdot}1$ with $NaNO_3$

[NaBr]	0·002	0·01	0·02	0·03	0·04	0·05	0·06	0·07	0·08
k obs.	6·78	6·53	6·88	6·60	6·65	5·48	5·73	5·50	5·40
k calc.	7·12	6·80	6·49	6·27	6·07	5·90	5·78	5·64	5·55

(*b*) 0·0277M-$HClO_4$, ionic strength made up to $I = 0{\cdot}135$ with $NaNO_3$

[NaBr]	0·0142	0·0337	0·0584	0·0829	0·107
k obs.	0·765	0·684	0·558	0·480	0·453
k calc.	0·792	0·663	0·561	0·495	0·447

nitrate at 25° by measuring the pH of a half-neutralized M/100-solution with a Cambridge pH-meter. Stable and reproducible readings were obtained, leading to $K_a = 1{\cdot}4 \times 10^{-3}$ at an ionic strength $I = 0{\cdot}2$.

[6] Bell, Everett, and Longuet-Higgins, *Proc. Roy. Soc.*, 1949, *A*, **197**, 141.
[7] *Org. Synth.*, 1933, **13**, 100.

XUM

The results of the kinetic measurements are given in Tables 1 and 2, in which k is the second-order velocity constant in equations (2)—(5), in l. mole^{-1} sec.$^{-1}$. Each value represents the mean of 3—8 experiments. In the acetate buffer solutions with the lowest bromide concentrations an appreciable proportion of the bromine is present as hypobromous acid. Bell and Spiro [1] suggested, on slender evidence, that hypobromous acid was about half as reactive as molecular bromine. This now seems improbable, and our own results are consonant with a negligible reactivity for hypobromous acid. The velocity constants in Table 1 have been corrected on this assumption: the maximum correction is only a few per cent.

TABLE 2. *Bromination of methyl methanetricarboxylate.*

Perchloric acid solutions, ionic strength made up to $I = 0{\cdot}2$ with $NaNO_3$.

[H$^+$]	[Br$^-$]	k (obs.)	k (calc.)	[H$^+$]	[Br$^-$]	k (obs.)	k (calc.)
0·00985	0·00554	7240	7370	0·0493	0·00554	1720	1710
	0·0499	5970	6120		0·0499	1400	1400
	0·0998	5410	5600		0·0998	1220	1240
	0·148	5210	5320		0·148	1150	1160
	0·188	5100	5170	0·0985	0·00554	1030	1000
0·0148	0·00554	5000	5000		0·0252	938	955
	0·0696	3890	3970		0·0499	811	798
	0·124	3720	3620		0·0745	782	740
	0·183	3520	3480		0·0893	770	712
0·0197	0·00553	3860	3810		0·0998	753	708
	0·0696	2900	3030	0·148	0·00553	767	765
	0·124	2790	2790		0·0204	655	688
	0·178	2710	2650		0·0351	603	637
0·0296	0·00554	2800	2640		0·0998	571	538
	0·0499	2190	2180				
	0·0998	2020	1970				
	0·168	1850	1910				

DISCUSSION

The values of k (calc.) for ethyl malonate in Table 1 are obtained from equation (2) with $K = 16{\cdot}0$, $k_2K_a = 2{\cdot}13 \times 10^{-4}$, $k_2'K_a = 1{\cdot}25 \times 10^{-4}$, $k_3K_E = 0{\cdot}93$, $k_3'K_E = 0{\cdot}154$. These values imply that bromination takes place predominantly through the enol at pH 2, and through the enolate ion at pH 5. There are no direct determinations of K_a or K_E for ethyl malonate, but if we use $K_a = 5 \times 10^{-14}$, $K_E = 10^{-5}$, as estimated by Bell and Spiro,[1] this gives $k_2 = 4{\cdot}3 \times 10^9$, $k_2' = 2{\cdot}5 \times 10^9$, $k_3 = 9{\cdot}3 \times 10^4$, $k_3' = 1{\cdot}5 \times 10^4$, all in l. mole^{-1} sec.$^{-1}$. These values are all of the same order of magnitude as those given by Bell and Spiro,[1] but only the first shows close agreement. The present values are to be preferred, since measurements were made at lower bromine concentrations, and no correction was necessary for the introduction of a second bromine atom.

The values of k (calc.) for methyl methanetricarboxylate correspond to $K = 16{\cdot}0$, $k_2K_a = 72{\cdot}0$, $k_2'K_a = 42{\cdot}3$, $k_3K_E = 320$, $k_3'K_E = 50$. For this substance a large proportion of the bromination takes place through the enolate ion even in 0·15M-perchloric acid, and the rate constants for the enol are not known very accurately. Our own measurements give $K_a = 1{\cdot}4 \times 10^{-8}$, whence $k_2 = 5{\cdot}2 \times 10^9$, $k_2' = 3{\cdot}0 \times 10^9$. K_E has not been measured in aqueous solution, but the pure ester contains 1·2% of enol.[8] This will certainly be reduced in aqueous solution, and we have assumed $K_E = 5 \times 10^{-3}$, giving $k_3 = 6 \times 10^4$, $k_3' = 1 \times 10^4$.

The velocity constants for bromination of the enolate anions are of the same order of magnitude as those found indirectly for the iodination of similar species,[2,3] and also directly for the bromination of phenoxide ions: [5] they are close to the maximum value expected for reactions in aqueous solution having zero energy of activation.[9,10] The corresponding velocity constants for the enols are lower by about four powers of ten, and again resemble

[8] Conant and Thompson, *J. Amer. Chem. Soc.*, 1932, **54**, 4039.
[9] Onsager, *J. Chem. Phys.*, 1934, **2**, 599.
[10] Debye, *Trans. Electrochem. Soc.*, 1942, **82**, 265.

those found for the iodination of enols and the bromination of phenols. It is noteworthy, however, that the relative reactivities of bromine and tribromide ion differ considerably in the two series.* In the present work $k(Br_3^-)/k(Br_2)$ was 0·6 for both enolate ions and 0·17 for both enols. On the other hand $k(Br_3^-)$ was only a few per cent of $k(Br_2)$ for the most reactive phenoxide ions, and could not be detected for phenol molecules or anisoles,[5] although the velocity constants for bromine resemble those in the present paper. As pointed out by Stock and Brown [11] and by Shatenshtein,[12] the selectivity of an organic molecule towards different reagents will decrease as the reactivity of the molecule increases, but it is clear that this principle can only be applied to a series of very similar molecules.

We thank Monsanto Chemicals Ltd. for a Fellowship awarded to D. J. R.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, September 26th,* 1960.]

* These relative reactivities are independent of the uncertainties in the absolute values arising from uncertainties in K_a and K_E.

[11] Stock and Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 3233, and earlier papers.
[12] Shatenshtein, *Zhur. fiz. Khim.*, 1960, **34**, 594.

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146. *The Cationic Polymerization of Styrene. Part I. The 1-Phenylethyl Cation.*

By D. O. JORDAN and F. E. TRELOAR.

Styrene and 1-phenylethyl alcohol dissolve in concentrated sulphuric acid–acetic acid mixtures to give yellow solutions. This coloration is attributed to the presence of the ions $PhMeHC^+$ and $Me{\cdot}CHPh{\cdot}OH_2^+$, the latter being the more stable. In solutions of 1-phenylethyl chloride and stannic chloride in 1,2-dichloroethane and of 1-phenylethyl chloride and aluminium chloride in carbon tetrachloride, the 1-phenylethyl ion also exists. This observation confirms the feasibility of many reaction mechanisms derived from kinetic data.

POLYMERIZATION of styrene by acids or Friedel–Crafts halides has been assumed generally to occur by a mechanism involving a carbonium ion as intermediate.[1] The carbonium ion is formed by addition to the olefin of a proton from the hydrogen acid or from a cocatalyst–halide complex. Theoretical calculations by Gold and Tye [2] and by Yonezawa *et al.*[3] suggest that the proton addition should bring about the formation of the 1-phenylethyl cation which would then be the initiating species of the polymerization. Until very recently there has been no direct evidence for the existence of this ion but only circumstantial evidence derived from studies of reaction mechanisms.[4]

Since it has been shown [5] that water is an essential cocatalyst for the polymerization of styrene by aluminium chloride, thus indicating that initiation must occur by proton addition, it became desirable to have more direct evidence for the existence of the 1-phenylethyl ion. We have measured the spectra of solutions of styrene in concentrated sulphuric acid (in which, from the conclusions of Gold and Tye,[6] it was to be expected that the 1-phenylethyl ion would be formed), as well as in certain organic solvents to determine whether the ion can exist under the conditions that occur during polymerization.

[1] Pepper, *Quart. Rev.*, 1954, **8**, 100.
[2] Gold and Tye, *J.*, 1952, 2184.
[3] Yonezawa, Higashimura, Katagiri, Hayashi, Okamura, and Fukui, *J. Polymer Sci.*, 1957, **26**, 311.
[4] Ward, *J.*, 1927, 445; Bergmann and Polanyi, *Naturwiss.*, 1933, **21**, 378; Hughes, Ingold, and Scott, *J.*, 1937, 1201, 1271; Bodendorf and Böhme, *Annalen*, 1935, **516**, 1; Hart, quoted by Streitwieser, *Chem. Rev.*, 1956, **56**, 622.
[5] Jordan and Treloar, *J.*, 737.
[6] Gold and Tye, *J.*, 1952, 2172.

XUM

Since this work was completed, Inoue and Mima [7] and Grace and Symons [8] have published spectra of styrene in sulphuric acid solution. The results of these authors, however, differ in detail from ours.

Experimental

Materials.—Commerical styrene was dried ($CaCl_2$), distilled at reduced pressure, and redistilled *in vacuo* three times, only the middle third being taken each time. 1-Phenylethyl alcohol was prepared by Grignard reaction from methylmagnesium bromide and benzaldehyde and fractionally distilled (b. p. 110°/15 mm.). Further distillation gave a product with an identical spectrum. 1-Phenylethyl chloride was prepared by Kharasch and Kleiman's method.[9] Stannic chloride (B.D.H.) was distilled *in vacuo* three times, the first half being rejected each time, and finally sealed in breakable phials. Aluminium chloride (B.D.H.) was mixed with its own volume of pure aluminium turnings, sublimed *in vacuo* through an 18 in. column of aluminium turnings, and collected in breakable phials as a white crystalline material. 1,2-Dichloroethane and carbon tetrachloride were commercial products purified by standard methods. Concentrated sulphuric acid and glacial acetic acid were analytical reagents.

Preparation of Solutions and Determination of Spectra.—(a) *Sulphuric acid.* Irreversible changes occur when styrene or 1-phenylethyl alcohol is added directly to sulphuric acid, for the reasons given by Grace and Symons.[8] Dilute solutions were therefore made in glacial acetic acid and then diluted ten-fold with concentrated sulphuric acid to give a final sulphuric acid concentration of 90% by volume. (Solutions in which the sulphuric acid concentration was 99% by volume gave identical results.) The spectra were measured on a Unicam S.P. 500 spectrophotometer by using matched 1 cm. silica cells with ground-glass stoppers and a sulphuric acid–acetic acid mixture of the same composition as the solvent as a reference. Since both the intensities and positions of the maxima changed with time, the complete spectrum for each solution was measured at three times after mixing and the initial spectrum determined by extrapolation, Gold and Tye's directions [6] being followed.

(b) *Organic solvents.* Stannic chloride and aluminium chloride solutions were made by cracking phials of the halide, dropping it into the solvent, and quickly stoppering the vessel. The solution was transferred in a closed system to a flask containing a measured amount of a solution of 1-phenylethyl chloride in the same solvent; it was then transferred to a dry spectrophotometer cell, again in a closed system, and the cell quickly stoppered. Water had to be excluded as completely as possible as the metal halides are readily hydrolysed. Solutions were kept at 25° until the maximum colour developed, and the spectra recorded as above.

Results and Discussion

Sulphuric Acid Solutions.—Solutions of styrene in concentrated sulphuric acid are yellow and quite different in their spectral behaviour from solutions in acetic acid. This is seen from a comparison of the curves in Fig. 1. It seems clear that a new species has arisen, probably from the protonation of styrene. A comparison was made with 1-phenylethyl alcohol in sulphuric acid solution and the spectrum of these solutions is shown in Fig. 2. The positions of the maxima and their intensities are given in Table 1. In the visible region the spectra of the two compounds are virtually identical; the dependence of the optical density on molar concentration is shown for the two solutes in Fig. 3. The wavelength of the maximum absorption in the visible region is 4300 Å, differing somewhat from the values of 4400 Å and 4350 Å obtained by Inoue and Mima [7] and Grace and Symons [8] respectively. The latter authors found that the extinction coefficient for this maximum was about 10,000, much higher than the value recorded in Table 1. Grace and Symons,[10] however, observed considerable variations in the value of the extinction coefficient and for some samples obtained values of about 1000 which is in agreement with the value given in Table 1.

[7] Inoue and Mima, *Chem. High Polymers (Japan)*, 1957, **14**, 402.
[8] Grace and Symons, *J.*, 1959, 958.
[9] Kharasch and Kleiman, *J. Amer. Chem. Soc.*, 1943, **65**, 11.
[10] Grace and Symons, personal communication.

TABLE 1. *The wavelength and extinction coefficients of the main absorption maxima of styrene and 1-phenylethyl alcohol in sulphuric acid.*

	Time (hr.)	Peak 1		Peak 2		Peak 3	
		λ	ε	λ	ε	λ	ε
Styrene	0	2700	1340	3080	1310	4300	1020
	5	2700	1490	3060	1340	4300	980
	24	2700	1780	3050	1410	4300	930
	78	2700	2410	3050 *	1360	4300	710
1-Phenylethyl alcohol	0	2700	1770	3050	1930	4300	1020
	½	2700	2130	3050 *	1540	4300	1020
	22	2700	2250	3050 *	1500	4300	930
	42	2700	2320	3050 *	1480	4300	900

* Shoulder.

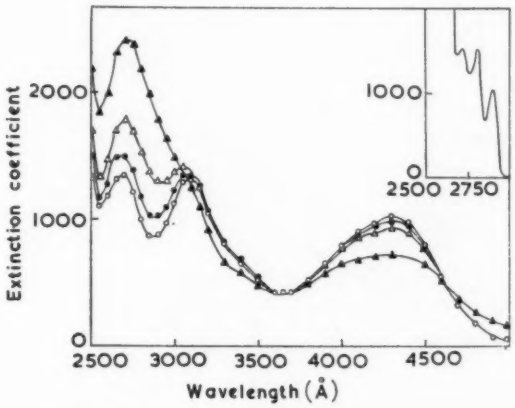


FIG. 1. *The spectrum of styrene in sulphuric acid.* ○ *initial curve obtained immediately after mixing,* ● *after* 5 *hr.,* △ *after* 24 *hr.,* ▲ *after* 78 *hr. Inset: spectrum of styrene in glacial acetic acid.*

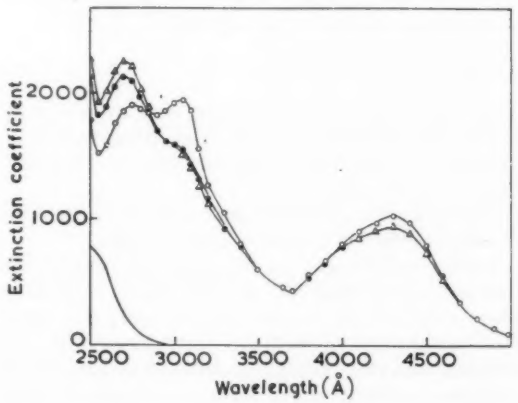


FIG. 2. *The spectrum of 1-phenylethyl alcohol in sulphuric acid.* ○ *initial curve obtained immediately after mixing,* ● *after* 0·5 *hr.,* △ *after* 22 *hr.:* — *spectrum in glacial acetic acid.*

The species formed was unstable and the peak at 4300 Å decreased with time, while the intensity of the peaks in the ultraviolet region increased. Reference to Table 1 shows that, at the same time, the position of peak 2 in the styrene spectrum changes and finally assumes the same value as for peak 2 in the spectrum of 1-phenylethyl alcohol. It is clear then that the identity of the visible spectra does not necessarily imply identity of the absorbing species as previous workers have assumed.

XUM

It is suggested that 1-phenylethyl alcohol ionizes initially as follows:

$$Me{\cdot}CHPh{\cdot}OH + H_2SO_4 \rightleftharpoons Me{\cdot}CHPh{\cdot}OH_2^+ + HSO_4^-$$

yielding an ion analogous to that formed by tertiary aliphatic alcohols in sulphuric acid rather than the free carbonium ion $PhMeHC^+$. This behaviour is identical with that of t-butyl alcohol in sulphuric acid,[11] and, since the bond energies of the corresponding chlorides and the kinetic evidence indicate that the t-butyl and the 1-phenylethyl ions

FIG. 3. *The dependence of the optical density (D_λ) on the concentration of solution in sulphuric acid:* ○ *styrene,* △ *1-phenylethyl alcohol.*

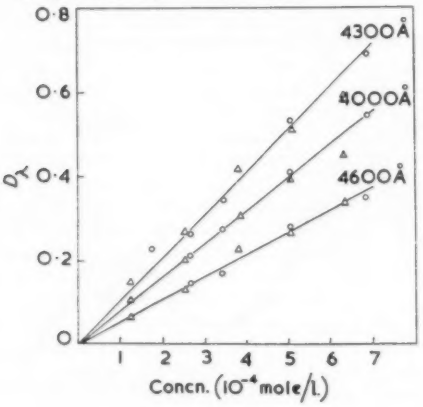
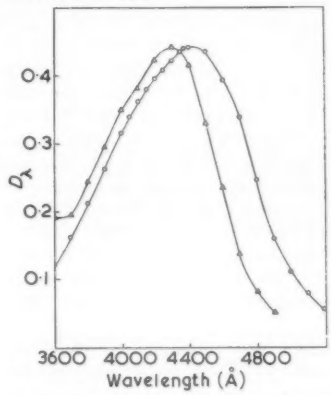


FIG. 4. *Comparison of the spectrum of styrene in sulphuric acid* ($4{\cdot}35 \times 10^{-4}$M) (△), *with that of 1-phenylethyl chloride* ($1{\cdot}22 \times 10^{-3}$M) *with* $SnCl_4$ ($2{\cdot}14 \times 10^{-1}$M) *in 1,2-dichloroethane* (○).



have similar stabilities, it is to be expected that the behaviour of the corresponding alcohols would also be similar. Styrene, however, can only ionize in one way, *viz.*:

$$CH_2{=}CHPh + H_2SO_4 \rightleftharpoons PhMeHC^+ + HSO_4^-$$

Since the solvent will contain some water, the carbonium ion formed from styrene may react with it to give the more stable ion $Me{\cdot}CHPh{\cdot}OH_2^+$ which is identical with that formed by the ionization of 1-phenylethyl alcohol. This process could explain the similarity of the two spectra after the lapse of a long time.

Ionization must be complete in each case since the absorption intensities were identical over a range of solvent composition from 60% to 99% of sulphuric acid by volume.

Solutions in Organic Solvents.—It is known that Friedel–Crafts halides will enhance the ionization of aralkyl halides.[12] Solutions of 1-phenylethyl chloride and stannic chloride in 1,2-dichloroethane develop a yellow colour which reaches a maximum intensity only after 25 hours at 25°. The absorption maximum occurs at 4400 Å; comparison with the spectrum of styrene in concentrated sulphuric acid (Fig. 4) suggests that, although there is a peak shift of 100 Å, the 1-phenylethyl ion is present in this solution. A similar peak shift occurs in the spectra of the triarylmethyl cations [14] in the same two solvents, where the shift is 40 Å. The optical density of the 4400 Å peak depends linearly on the concentrations of 1-phenylethyl chloride and stannic chloride, as shown in Fig. 5. If Beer's

[11] Hantzsch, *Z. phys. Chem.*, 1908, **65**, 41; Newman, Craig, and Garrett, *J. Amer. Chem. Soc.*, 1949, **71**, 869.
[12] Fairbrother and Wright, *J.*, 1949, 1058; Bayles, Evans, and Jones, *J.*, 1957, 1020.
[13] Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1956, **52**, 332.
[14] Evans, McEwan, Price, and Thomas, *J.*, 1955, 3098.

law holds for this peak in 1,2-dichloroethane, as in sulphuric acid, this means that the total ionic concentration is equal to K[Me·CHPhCl][$SnCl_4$] and the equilibrium

$$Me{\cdot}CHPhCl + SnCl_4 \rightleftharpoons (PhMeHC^+)(SnCl_5^-) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

is operating. The lack of any marked curvature indicates that any separation of the ion-pair must be slight.

The ionic concentrations have been calculated by assuming that the molar extinction coefficient of the ion is the same for 1,2-dichloroethane solutions as for sulphuric acid

FIG. 5. *Dependence of the optical density ($D\lambda_{max.}$) on concentration of reagents:* ● *1-phenylethyl chloride* ($SnCl_4$ *concn.* $5{\cdot}01 \times 10^{-2}$M); ▲ $SnCl_4$ (*1-phenylethyl chloride concn.* $5{\cdot}26 \times 10^{-2}$M).

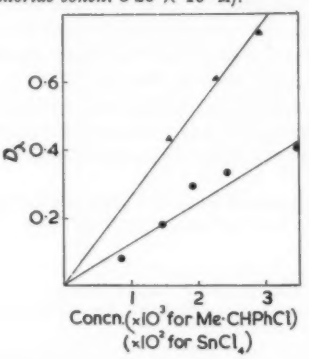


FIG. 6. *Variation of the concentration product,* [Me·CHPhCl][$SnCl_4$], *with total ionic concentration.*

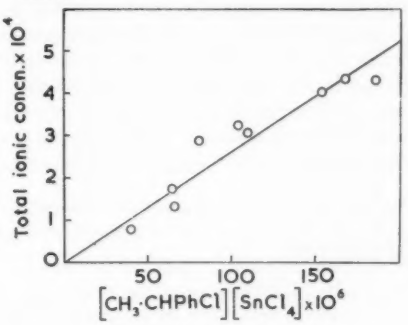


FIG. 7. *Variation of optical density and* log K *with* $1/T$ *for the equilibrium between 1-phenylethyl chloride and* $SnCl_4$ *in 1,2-dichloroethane.*

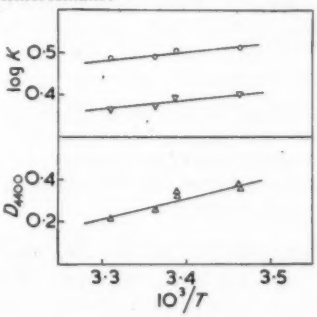
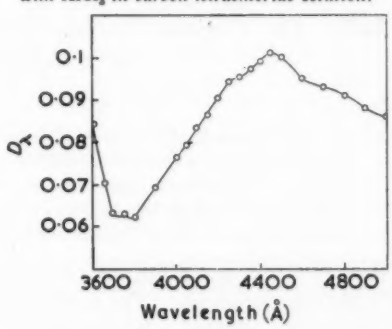


FIG. 8. *The spectrum of 1-phenylethyl chloride with* $AlCl_3$ *in carbon tetrachloride solution.*



solutions. A similar assumption has been proved true for solutions of triarylmethyl ions in the solvents *m*-cresol,[14] formic acid,[15] and nitromethane.[16] The ionic concentration has been plotted against the product of the equilibrium concentrations of Me·CHPhCl and $SnCl_4$ in Fig. 6, and the slope of the line obtained gives a value of 2·68 l. mole^{-1} for the equilibrium constant of reaction (1). It has been assumed that the activity coefficients of the reacting species are unity, since 1-phenylethyl chloride and the ion-pair are present in concentrations of 10^{-3}M and 10^{-4}M, respectively, and solutions of stannic chloride in 1,2-dichloroethane should approach ideality because of structural similarities. The value

[15] Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1954, **50**, 568.
[16] Bayles, Cotter, and Evans, *J.*, 1955, 3104.

XUM

of ΔG° for this reaction is then −0·59 kcal./mole. Fig. 7 shows the variation of log D_{4400} against $1/T$ corrected for the expansion of the solvent, and also the variation of log K with $1/T$. The slope of the straight line gives a value for ΔH° of −0·006 kcal./mole, whence $\Delta S^\circ = -2$ cal. degree^{-1} mole^{-1}. The ionization of the triarylmethyl halides is always accompanied by a decrease in entropy [12-16] and hence the value obtained here is added evidence that ions are formed.

Solutions of 1-phenylethyl chloride and stannic chloride in carbon tetrachloride, however, showed no measurable absorption in the region of 4400 Å even after several days. This is to be expected, since it has been shown [17] that carbon tetrachloride is too weakly polar to permit the formation of the more stable triphenylmethyl ion arising from triphenylmethyl chloride and stannic chloride. However, when aluminium chloride was used in place of stannic chloride, a yellow colour developed in the solution, giving the visible absorption spectrum shown in Fig. 8 with the maximum at 4450 Å. The similarity of shape to that of styrene in sulphuric acid and 1-phenylethyl chloride in 1,2-dichloroethane suggests that it is due to the 1-phenylethyl ion also. Aluminium chloride would be expected to be more effective in promoting ionization than stannic chloride in view of its greater acid strength. However, the possibility of aluminium chloride molecules' helping to solvate the ion-pair must not be ignored, since it is known that mercuric chloride behaves in this manner towards triarylmethyl halides in benzene and chlorobenzene solution.[12]

One of us (F. E. T.) thanks the Commonwealth Scientific and Industrial Research Organisation for the award of a Senior Australian Studentship during the work described here and in Parts II and III.

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The University of Adelaide, South Australia. [*Received, April 20th*, 1960.]

[17] Bonner, Clayton, and Gwyn Williams, *J.*, 1958, 1705.

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147. *The Cationic Polymerization of Styrene. Part II.*[1] *Spectra of Polymerizing Systems.*

By D. O. Jordan and F. E. Treloar.

Solutions of styrene and stannic chloride or aluminium chloride in 1,2-dichloroethane or carbon tetrachloride are coloured and polymerization takes place. It is shown that this colour is due to the presence of the 1-phenylethyl cation and the styrene polymer ion. This confirms the suggested mechanism for the polymerization of styrene by such catalysts.

In Part I,[1] it was shown that the 1-phenylethyl ion can exist in both 1,2-dichloroethane and carbon tetrachloride. The methods described there have been extended in order to investigate the coloured solutions formed when styrene is polymerized by using Friedel–Crafts halides as catalysts in an attempt to discover the nature of the intermediates present.

Experimental.—Materials. Styrene, 1-phenylethyl chloride, 1,2-dichloroethane, carbon tetrachloride, and stannic chloride were purified as in Part I.[1] Aluminium chloride was prepared from aluminium and silver chloride by a modification of the method of Wallace and Willard [2] or as described in Part I. The two samples gave similar spectroscopic results.

Solutions were made up and measured, as described in Part I, for organic solvents.

Results.—The spectra of the coloured solutions formed when styrene is polymerized by aluminium chloride in carbon tetrachloride and 1,2-dichloroethane are shown in Fig. 1. The

[1] Part I, Jordan and Treloar, preceding paper.
[2] Wallace and Willard, *J. Amer. Chem. Soc.*, 1950, **72**, 5275.

absorption maxima occur at 4200 and 4450 Å in carbon tetrachloride and 4100 Å in 1,2-dichloroethane. To elucidate the nature of the last peak, the spectrum of the system styrene–1-phenylethyl chloride–stannic chloride–1,2-dichloroethane was studied. The solutions immediately developed an intense yellow colour and polymerization occurred as shown by precipitating the polymer with methanol at various times. The results of the measurement of the absorption spectra for a typical experiment are shown in Fig. 2. In solutions containing both styrene and 1-phenylethyl chloride, a peak immediately developed at 4100 Å closely similar to that shown in Fig. 1 for the system styrene–aluminium chloride–1,2-dichloroethane. The value of this maximum remained constant for at least 12 hr. and thereafter gradually decreased. A solution containing the same concentration of 1-phenylethyl chloride, but no styrene, gradually developed the 4400 Å peak characteristic of the 1-phenylethyl ion. A

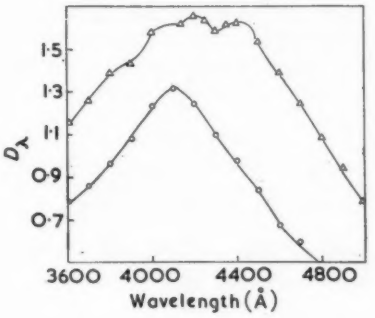

FIG. 1. *The spectra of polymerizing systems:*
○ *styrene–$AlCl_3$–1,2-dichloroethane.*
△ *styrene–$AlCl_3$–carbon tetrachloride.*

solution containing only styrene at the same concentration as in the mixed solution immediately developed a very pale yellow colour; the maximum was hard to define but occurred at about 4100 Å.

Discussion.—It is suggested that the peak at 4100 Å in 1,2-dichloroethane is due to the growing polymer ion $Me{\cdot}CHPh{\cdot}[CH_2{\cdot}CHPh]_n{\cdot}CH_2{\cdot}\overset{+}{C}HPh$. This cannot be derived initially from a reaction between $PhMeHC^+$ and styrene since it is present in stationary concentration from the start of the reaction, when the concentration of 1-phenylethyl carbonium ions is negligible. Hence the initial reaction to form this ion must be either a combination of a 1-phenylethyl chloride–$SnCl_4$ complex with styrene, which subsequently forms the growing ion pair, or a termolecular reaction of styrene, 1-phenylethyl chloride, and $SnCl_4$. No free $PhMeHC^+$ ions are formed in the system, as shown by comparison with the spectrum of the same system which contains no styrene. After 18 hr. the concentration of 1-phenylethyl ions is very great indeed, but the system containing styrene shows only a slight fall-off in optical density due to the gradual cessation of polymerization.

In the total absence of 1-phenylethyl chloride, a very weak peak occurred at 4100 Å which, by comparison with solution 1 (Fig. 2), is to be attributed to the presence of the polymer ion. This will be formed since water is undoubtedly present and hence polymerization will be proceeding. The suggestion by Devlin and Pepper [3] that this is due to a complex between the olefin and stannic chloride is now untenable; their observation that the colour is destroyed by solvents which form strong complexes is most readily explained by the destruction of the ion by such solvents.

This interpretation of the results is in substantial agreement with the results of Colclough and Dainton [4] on the polymerization of styrene by stannic chloride in 1,2-dichloroethane

[3] Devlin and Pepper, "Cationic Polymerization and Related Complexes," ed. P. H. Plesch, Heffer, Cambridge, 1953, p. 24.
[4] Colclough and Dainton, *Trans. Faraday Soc.*, 1958, **54**, 901.

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with t-butyl chloride as cocatalyst. These authors suggested that the initial step in the reaction is either a reaction of the monomer with a catalyst–cocatalyst complex or a termolecular reaction. Since the 1-phenylethyl and t-butyl cations have nearly equal stabilities, the two systems are directly comparable. From the results presented here it is not possible to distinguish between the two possibilities suggested by Dainton and Colclough, but it is clear that no ions are involved in the initial step.

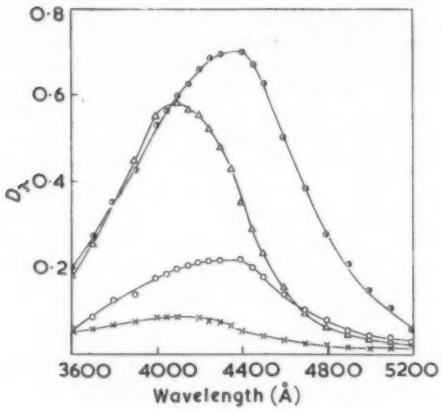

FIG. 2. *The spectra, in* 1,2-*dichloroethane, of the systems*: × *styrene* ($4{\cdot}22 \times 10^{-2}$M) *and* $SnCl_4$ ($1{\cdot}74 \times 10^{-1}$M) *after* 0·5 *and* 1·5 *hr.*, △ *styrene* ($4{\cdot}22 \times 10^{-2}$M), $SnCl_4$ ($1{\cdot}74 \times 10^{-1}$M), *and* 1-*phenylethyl chloride* ($8{\cdot}14 \times 10^{-3}$M) *after* 0·5 *and* 1·5 *hr.*; 1-*phenylethyl chloride* ($8{\cdot}14 \times 10^{-3}$M) *and* $SnCl_4$ ($1{\cdot}74 \times 10^{-1}$M), ○ *after* 0·5 *hr.*, ◑ *after* 1·5 *hr.*

In the carbon tetrachloride solution the 4450 Å peak must be attributed to the 1-phenylethyl carbonium ion in accordance with Part I,[1] while the 4200 Å peak is clearly due to the growing polymer ion. The Table, which summarizes the spectroscopic data on the two

Wavelength of maximum absorption for 1-*phenylethyl cation and growing polymer ion.*

Solvent	$PhMeHC^+$	Polymer ion
Sulphuric acid	4300	<4160 *
1,2-Dichloroethane	4400	4100
CCl_4	4450	4200

* The absorption maximum for 1,3-diphenylbut-1-ene or the styrene dimer in concentrated sulphuric acid [Inoue and Mima, *Chem. High Polymers* (*Japan*), 1957, **14**, 402].

ions, shows clearly that solvent effects are the same in each case. It is interesting that the spectra show that both the 1-phenylethyl ion and the polymer ion exist together in carbon tetrachloride solution in agreement with some kinetic data [5] which suggest that preliminary ionization is rate-determining. Furthermore, the results on solutions in 1,2-dichloroethane indicate that there does exist a stationary concentration of growing chains, at least in this case, thus confirming an assumption universally made in investigations of polymerization kinetics.

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[5] Jordan and Treloar, unpublished results.

148. *The Cationic Polymerization of Styrene. Part III.*[1] *The Co-catalytic Action of Water in the Polymerization of Styrene by Aluminium Chloride.*

By D. O. Jordan and F. E. Treloar.

By using very carefully dried styrene and pure aluminium chloride, it has been shown that water is necessary for the polymerization.

The observation by Jordan and Mathieson [2] that styrene is polymerized by aluminium chloride in carbon tetrachloride solution in the absence of a cocatalyst is at variance with the proton-addition theory of Polanyi *et al.*[3] which has been found to hold for several other metal halide catalyst systems. Jordan and Mathieson claimed that the system was anhydrous, and hence that initiation occurred through a π-complex between the olefin and aluminium chloride. This system has been re-investigated under conditions designed to give more stringent drying than previously obtained in order to eliminate the possible cocatalytic action of traces of water.

Experimental.—Materials. A commercial sample of styrene was redistilled and kept over sodium wire which was frequently crushed to expose fresh surfaces. It was then distilled three times *in vacuo*, only the middle third being taken each time, before finally being distilled on to outgassed barium oxide and stored for two weeks.

Aluminium chloride was prepared by Wallace and Willard's method,[4] using pure aluminium turnings and silver chloride made from "AnalaR" reagents. This was sublimed without residue into breakable phials as a white crystalline material.

Apparatus and procedure. A vacuum-line similar to that of Brackman and Plesch [5] was used. After being pumped out with frequent flamings for several days at a pressure less than 10^{-3} mm. the system was shut off from the line, the aluminium chloride phial broken, and styrene distilled from barium oxide on to the aluminium chloride, a cold trap being used. On melting, the styrene was observed to run over the white aluminium chloride with no polymerization and the formation of a very pale straw colour. The styrene could be distilled off, leaving no trace of polymer. On admission of water vapour a bright orange colour developed at the aluminium chloride–styrene interface and polymerization occurred. Larger quantities of water discharged the colour.

Discussion.—These results are in agreement with some otherwise inconclusive kinetic results [6] on the system styrene–aluminium chloride–carbon tetrachloride in which the drying of reagents, although not sufficient to stop polymerization, showed that the polymerization rate was below that obtained by Jordan and Mathieson.[2] The orange colour on addition of water is due to the formation of the 1-phenylethyl ion and the growing polymer ion.[1] It is clear that polymerization must be initiated by proton addition to the styrene and hence water is a cocatalyst. Excess of water discharges the colour because of the known reactivity of carbonium ions.

The system aluminium chloride–styrene–carbon tetrachloride is now in conformity with other polymerizations catalysed by metal halides, since in all systems studied up to the present, the presence of a cocatalyst is essential for reaction to proceed.

Department of Physical and Inorganic Chemistry, The Johnson Laboratories, University of Adelaide, South Australia. [*Received, April 20th*, 1960.]

[1] Part II, preceding paper.
[2] Jordan and Mathieson, *J.*, 1952, 611, 621.
[3] Polanyi, Evans, Holden, Plesch, Skinner, and Weinberger, *Nature*, 1946, **157**, 102.
[4] Wallace and Willard, *J. Amer. Chem. Soc.*, 1950, **72**, 5275.
[5] Brackman and Plesch, *J.*, 1953, 1289.
[6] Treloar, Thesis, University of Adelaide, 1958.

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149. *The Structure of "Cyclopropane Platinous Chloride."* [1]

By D. M. Adams, J. Chatt, R. G. Guy, and N. Sheppard.

The substance of composition $(C_3H_6Cl_2Pt)_n$ (I), formed from hexachloroplatinic acid and cyclopropane, is shown to be a chloride-bridged polymer built from dichloro(trimethylene)platinum(IV) (III). Pyridine reacts with complex (I) to form the hexaco-ordinated compound dichloro(trimethylene)-dipyridineplatinum(IV) (II). Tertiary phosphines (PR_3) displace cyclopropane from the complexes (I) and (II), reducing the platinum atom to the bivalent state, and forming a mixture of *cis*- and *trans*-$[PtCl_2(PR_3)_2]$. Cl^-, I^-, and CN^- behave similarly.

The infrared and nuclear magnetic resonance spectra of the complexes are consistent with the proposed structures.

Olefins and acetylenes readily form complexes with salts of silver(I), copper(I), mercury(II), and platinum(II).[2] In these complexes the hydrocarbon is bonded to the metal atom by interaction of the delocalised π-electrons of the C:C or C:C bond with a suitable orbital of the metal atom.[3] Following the suggestion by Walsh [4] that there is considerable delocalisation of the electrons of the cyclopropane ring, Tipper [5] examined the ability of cyclopropane to form similar complexes. He reported that cyclopropane reacts with hexachloroplatinic acid (H_2PtCl_6) in acetic anhydride to form a brown solid of the composition $C_3H_6Cl_2Pt$ (I), which gives a white compound $[PtCl_2(C_3H_6)(py)_2]$ (II) on treatment with pyridine (py). Cyclopropane is liberated quantitatively from both these compounds by aqueous potassium cyanide. This, and the fact that the infrared spectrum of compound (I) showed only two C–H stretching frequencies, led Tipper to suggest that the cyclopropane ring is intact in these complexes. He considered cyclopropane to behave as an unsaturated ligand, like ethylene, and compound (I) to be a dimer analogous to ethyleneplatinous chloride, $[Pt_2Cl_4(C_2H_4)_2]$, with its platinum atoms in the bivalent state.

However, unlike ethyleneplatinous chloride, compound (I) is insoluble in all the usual organic solvents except ethanol, in which its limited solubility varies from sample to sample and depends on the previous history of the sample. This property suggests that compound (I) is a polymer, $[PtCl_2(C_3H_6)]_n$. Furthermore, compound (I) is formed by salts of platinum(IV), *e.g.*, platinic chloride and hydrogen hexachloroplatinate, but not by salts of platinum(II), *e.g.*, sodium and potassium tetrachloroplatinate, and the stoicheiometry of the complex (II) does not accord with the chemistry of olefin–platinum(II) complexes, which give complexes of the type *trans*-$[PtCl_2(olefin)(amine)]$ on treatment with amines. We have, therefore, re-investigated the structures of compounds (I) and (II) and conclude on the basis of their chemistry and infrared and nuclear magnetic resonance spectra that compound (I) is a polymer built from units of dichloro(trimethylene)platinum(IV) (III), in which the cyclopropane ring has opened and chelated to the platinum atom. The polymerisation of the unit (III) must occur through chloride bridges whereby the platinum-(IV) atom achieves its normal co-ordination number of six.

The white compound (II) is dichloro(trimethylene)dipyridineplatinum(IV), formed by the normal bridge-splitting reaction of pyridine with the chloride-bridged polymer (I). It is stable, readily soluble in organic solvents, monomeric, a non-electrolyte in nitrobenzene, and diamagnetic, and has a dipole moment of 6·05 D. Three geometric isomers are possible, *i.e.*, (IV), (V), and (VI) and tentatively, on the basis of the infrared spectrum, this white

[1] For a preliminary communication, see Adams, Chatt, Guy, and Sheppard, *Proc. Chem. Soc.*, 1960, 179.

[2] See Keller, *Chem. Rev.*, 1941, **28**, 229; Helmkamp, Carter, and Lucas, *J. Amer. Chem. Soc.*, 1957, **79**, 1306; Chatt, Duncanson, and Guy, *Chem. and Ind.*, 1959, 430.

[3] See Chatt and Duncanson, *J.*, 1953, 2939.

[4] Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179; cf. Coulson and Moffitt, *Phil. Mag.*, 1949, **40**, 1.

[5] Tipper, *J.*, 1955, 2045.

compound has been assigned the *trans*-configuration (IV). The dipole moment is consistent with this but does not distinguish between structures (IV) and (V). It isomerises in boiling benzene to a bright yellow solid (VII) which was examined only cursorily owing to the difficulty in obtaining reproducible samples. This solid is monomeric, diamagnetic, and a non-electrolyte in nitrobenzene. It may be one of the other two possible stereoisomers of complex (II), or a mixture of both, although its spectra and chemical reactions differ so much from those of compound (II) that a more extensive re-arrangement may have occurred.

Unsuccessful attempts were made to prepare compound (II) by treatment of cyclopropane with *cis*- and *trans*-$[PtCl_2(py)_2]$ and *cis*- and *trans*-$[PtCl_4(py)_2]$ (py = pyridine).

The 2,2′-bipyridyl analogue of compound (II), *i.e.*, $[PtCl_2(C_3H_6)$ (bipy)], was prepared by the reaction of bipyridyl (bipy) with the polymer (I). It is cream-coloured, and insoluble in all common solvents. Tertiary phosphines (PR_3) do not give analogues of compound (II), but form *trans*- and/or *cis*-$[PtCl_2(PR_3)_2]$ with liberation of cyclopropane (identified by its infrared spectrum).

The liberation of cyclopropane with simultaneous reduction to platinum(II) is a general reaction of anionic ligands of high *trans*-effect, and it appears that the three-carbon chain is freed in such a manner by these ligands that it cyclises during the liberation reaction.

$$(II) + 2NaI \xrightarrow{\text{Acetone}} [PtI_2(py)_2] + C_3H_6 + 2NaCl$$

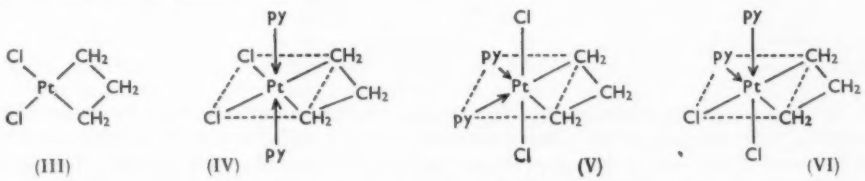
$$(I) + 4KCN \xrightarrow{H_2O} K_2[Pt(CN)_4] + C_3H_6 + 2KCl$$

The pyridine derivative (VII) differs from compound (II) in giving no gaseous product even with boiling potassium cyanide solution.

Chlorides reacted only slowly with compounds (I) and (II), sometimes with elimination of the C_3H_6 residue, although the form in which it was liberated was not determined. Thus compound (I) dissolved slowly in aqueous hydrochloric acid and in aqueous sodium chloride; and on addition of $[Pt(NH_3)_4][ClO_4]_2$, Magnus's salt, $[Pt(NH_3)_4][PtCl_4]$, was isolated. Compound (II) behaved similarly in aqueous solution, but in ethereal solution the complex $[pyH]^+[PtCl_3(C_3H_6)(py)]^-$ was formed.

On thermal decomposition the compound (I) gave mainly an unidentified mixture of chlorinated hydrocarbons together with traces of hydrogen chloride and cyclopropane, but no propene that could be detected by infrared analysis. On the other hand, the pyridine derivatives (II) and (VII) gave high yields of propene, containing in the case of compound (II) traces of cyclopropane and pyridine.

Infrared spectra of compounds (I) and (II) and of cyclopropane are recorded in the Table. The spectrum of the complex (I) is more complicated than, and bears no relation to, that of cyclopropane.



When a hydrocarbon is attached as an uncharged ligand to a metal atom, as in Zeise's salt, $K[PtCl_3(C_2H_4)],H_2O$,[6] or dibenzenechromium,[7] the infrared spectrum of the ligand in the complex is similar to that of the free ligand. If, therefore, cyclopropane were bonded to the platinum atom as a ring, its local symmetry would be largely preserved ($D_{3h} \longrightarrow C_{3v}$) and its spectrum should exhibit bands similar in number and position to

[6] Powell and Sheppard, *Spectrochim. Acta*, 1958, **13**, 69.
[7] Snyder, *Spectrochim. Acta*, 1959, 807.

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those of the gas. That this is not so must mean that the cyclopropane ring has opened and that one or two platinum–carbon σ-bonds have been formed. If only one σ-bond were formed, the C_3 chain would probably end with a CH_3, CH_2Cl, or $=CH_2$ group. All three possibilities are clearly ruled out by the spectrum. A sensitive indication of environment is provided by the C–H stretching frequencies. For compound (I) these lie at 3025, 2954, and 2948sh cm.$^{-1}$, which are values intermediate between those of cyclopropane (3103, 3028 cm.$^{-1}$) and open-chain hydrocarbons. Thus, the infrared spectrum is clearly in favour of structure (III) for compound (I). A reasonable assignment of the observed bands can be made on this basis and is included in the Table together with the band positions.

Assignment of bands due to C_3H_6 unit	$[PtCl_2(C_3H_6)]$	$[PtCl_2(C_3H_6)(py)_2]$ (white isomer)	Cyclopropane [a]
		3100vw *	
		3070w *	
		3040vw *	
		3007w *	3102·9
C–H	3025m	2992w	3028·1
	2954m	2938m	
	2948sh	2917m	
		1600s *	
		1565vw *	
		1481m *	
		1444vs *	1441·8
CH_2 deformation	1414m	1437sh	
		1406vw *	
		1380vw *	
		1350w *	
		1250w *	
CH_2 wag	1255s	1238w	
	1237sh		
CH_2 twist	1165w	1217m	
		1195s *	
		1153w *	
Ring deformation	1149s	1134w	
	1125w	1087w	
		1064s *	
CH_2 rock	1087vs	1038s	
	1022vw		1028·7
		1011s *	
Ring deformation	981m	980vw	
CH_2 rock	948m	976w	
		941w *	
	890w	892w	
		873w *	868·5
		756vs *	
		691vs *	
	663w,b		
		632s *	
Ring deformation (Mainly Pt–C)	563m		

* Bands due to co-ordinated pyridine.

In the case of the white isomer (II), the spectrum is complicated by the presence of pyridine. By comparison with the spectra of several pyridine complexes of platinum(IV) the pattern of absorption due to pyridine was traced in complex (II), and the remaining bands assigned to the C_3H_6 unit. It is clear that the cyclopropane ring is not intact and the absorption due to C_3H_6 compares reasonably with that found in compound (I) although there are some shifts of frequency and intensity.

The *trans*-configuration of the pyridine ligands in complex (II) was inferred from the absence of splitting of the strong pyridine bands at 756 and 691 cm.$^{-1}$. The complexes *trans*-$[PtCl_4(py)_2]$ and *trans*-$[PtCl_2(py)_2]$ also have very strong single bands, near 760 and

[a] Baker and Lord, *J. Chem. Phys.*, 1955, **23**, 1636.

680 cm.$^{-1}$. In *cis*-$[PtCl_4(py)_2]$ the band near 680 cm.$^{-1}$ splits into two, whilst in *cis*-$[PtCl_2(py)_2]$ both bands split into two.

The spectrum of the yellow solid (VII) is more complex than that of compound (II). In particular, extra bands were found near 1600 cm.$^{-1}$ and in the 780—680 cm.$^{-1}$ region, in which absorption characteristic of the pyridine molecule occurs. This is consistent with a *cis*-arrangement of pyridine ligands as in (V) or (VI).

Nuclear Magnetic Resonance Spectra.—The spectrum of the white isomer of compound (II) has been discussed previously [1] and was shown to support the structural formula (IV). The yellow isomer (or mixture of isomers) (VII) gave a rather weak spectrum owing to limited solubility in chloroform. In addition to hydrogen resonances attributable to the pyridine ligands, two main bands were observed. These consisted of a clearly defined triplet at $\tau = 9{\cdot}07$ [tetramethylsilane ($\tau = 10{\cdot}00$) was used as internal standard [9]] ($J_{HH'} \sim 7$ c./sec.), and a broader and weaker band with poorly resolved structure at $\tau \sim 7{\cdot}9$. The former band is of the strength and has the fine structure expected from the CH_2–[Pt] group,[1] and the latter might well represent the central $[CH_2]{\cdot}CH_2{\cdot}[CH_2]$ group in a $[CH_2]_3Pt$ ring. In the spectrum of the white isomer, both types of methylene group had a chemical shift of $\tau = 7{\cdot}5$; the notable change in position of the resonance of the terminal methylene in (VII) seems most likely to be connected with their different relative locations with respect to the highly magnetically anisotropic pyridine ligands. If this is so, the persisting chemical equivalence of the $CH_2{\cdot}$[Pt] groups implies that they are possibly symmetrically located with respect to the pair of pyridine rings and that if compound (VII) is a geometric isomer of (II) the more likely configuration is (V).

Unsuccessful attempts were made to prepare complexes from cyclopropane and sodium hexabromoplatinate, sodium tetra- and hexa-chloropalladate, or rhodium trichloride. Solutions of hydrogen hexachloroplatinate and cyclopropyl methyl ketone or dicyclopropyl ketone in acetic anhydride rapidly decomposed, yielding amorphous black solids. Cyclopentane and cyclohexane reacted with hydrogen hexachloroplatinate in acetic anhydride to give amorphous black solids which contained carbon and hydrogen in the approximate ratio of 1 : 2. Attempts to prepare the cyclobutyl and cyclopentyl analogues of compounds (I) and (II) by reaction of $Li{\cdot}[CH_2]_n{\cdot}Li$ ($n = 4$ or 5) with *cis*- or *trans*-$[PtCl_4(py)_2]$ and with platinic chloride gave no identifiable products.

Experimental

Microanalyses were carried out in these laboratories. Cyclopropane was obtained from the British Oxygen Company.

Catenadi-μ-chloro(trimethylene)platinum(IV) (I).—This was prepared from hydrogen hexachloroplatinate in 50—70% yield as described; [5] it decomposed at ~148° without melting (Found: C, 11·75; H, 1·95. Calc. for $C_3H_6Cl_2Pt$: C, 11·7; H, 1·95%). It can be prepared in similar yield from platinum tetrachloride. The colour of samples from apparently identical preparations varied from light yellow to dark brown.

Reactions of Catenadi-μ-chloro(trimethylene)platinum(IV) (I).—(a) *With pyridine.* The complex (I) was dissolved, with cooling, in pyridine, and dichloro(trimethylene)dipyridineplatinum-(IV) was isolated in 70—80% yield by dilution with water. Recrystallisation of the complex from cold chloroform gave colourless prisms, m. p. 140—145° (decomp.) [Found: C, 33·2; H, 3·65; N, 6·1%; *M* (cryoscopic in 0·504% benzene solution), 493. Calc. for $C_{13}H_{16}Cl_2N_2Pt$: C, 33·5; H, 3·45; N, 6·0%; *M*, 466].

(b) *With 2,2′-bipyridyl.* A suspension of dichloro(trimethylene)platinum(IV) (0·803 g., 1 mol.) in ethanol (25 ml.) was treated with a solution of 2,2′-bipyridyl (0·406 g., 1 mol.) in ethanol (20 ml.). *Dichloro(trimethylene)-2,2′-bipyridylplatinum*(IV) separated immediately as a cream-coloured solid (1·135 g., 95%), m. p. 340—355° (decomp.) (Found: C, 33·2; H, 3·25; N, 5·85. $C_{13}H_{14}Cl_2N_2Pt$ requires C, 33·65; H, 3·05; N, 6·05%). This compound is insoluble in water and all the common organic solvents.

(c) *With triethylphosphine.* A suspension of dichloro(trimethylene)platinum(IV) (1·685 g.,

[9] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

XUM

1 mol.) in ethanol (20 ml.) was treated under nitrogen with triethylphosphine (1·290 g., 2 mol.). The resulting clear yellow solution was taken to dryness, and the buff-coloured, crystalline residue (2·74 g.) treated with light petroleum (b. p. 60—80°). After removal of the solvent, the soluble fraction (0·74 g., 27%) crystallised from methanol as light yellow prisms, m. p. 142—143° undepressed on admixture with *trans*-bis(triethylphosphine)dichloroplatinum(II) (Found: C, 28·85; H, 6·0. Calc. for $C_{12}H_{30}Cl_2P_2Pt$: C, 28·7; H, 6·0%). The fraction (2·00 g., 73%), insoluble in light petroleum, crystallised from methanol as colourless prisms, m. p. 190—192° undepressed on admixture with *cis*-bis(triethylphosphine)dichloroplatinum(II) (Found: C, 28·8; H, 6·0%).

(d) *With triphenylphosphine.* On similar treatment with triphenylphosphine the complex (I) gave *cis*-bis(triphenylphosphine)dichloroplatinum(II), m. p. 300—310° (decomp.), in quantitative yield (Found: C, 54·55; H, 3·9. Calc. for $C_{36}H_{30}Cl_2P_2Pt$: C, 54·7; H, 3·8%).

(e) *With aqueous hydrochloric acid.* The complex (I) (0·308 g., 1 mol.) was dissolved in 12N-hydrochloric acid (10 ml.), giving a clear yellow solution which was diluted with water (20 ml.) and treated with tetrammineplatinum(II) perchlorate $[Pt(NH_3)_4][ClO_4]_2$ (0·462 g., 1 mol.) in water (20 ml.). Dark green prisms of Magnus's salt (0·483 g.) were formed over a period of 2 weeks (Found: C, 0·0; H, 2·2; N, 9·15. Calc. for $H_{12}Cl_4N_4Pt_2$: C, 0·0; H, 2·0; N, 9·35%).

Reactions of Dichloro(trimethylene)dipyridineplatinum(IV) (II).—(a) *With triphenylphosphine.* The complex (II) (0·466 g., 1 mol.) in benzene (30 ml.) was treated with a solution of triphenylphosphine (0·500 g., 1·9 mol.) in benzene (10 ml.). A yellow colour developed immediately and *cis*-bis(triphenylphosphine)dichloroplatinum(II) (0·733 g.), m. p. 305—315° (decomp.), separated in cream-coloured prisms (Found: C, 54·75; H, 3·9%).

(b) *With sodium iodide.* The complex (II) (0·466 g., 1 mol.) and sodium iodide (0·900 g., 6 mol.) in acetone (20 ml.) were heated under reflux for 30 min. The solid obtained on evaporation of the solvent was dissolved in a large volume of hot chloroform, and addition of light petroleum (b. p. 60—80°) gave di-iododipyridineplatinum(II) as yellow prisms, m. p. 287—288° (decomp.) (Found: C, 19·75; H, 1·85; N, 4·25. Calc. for $C_{10}H_{10}I_2N_2Pt$: C, 19·8; H, 1·65; N, 4·6%).

(c) *With aqueous hydrochloric acid.* The complex (II) (0·295 g.) dissolved slowly in 12N-hydrochloric acid (10 ml.), giving a yellow solution. On addition of tetrammineplatinum(II) perchlorate (0·285 g.) the pink form of Magnus's salt (0·240 g.) immediately separated (Found: C, 0·0; H, 2·2; N, 9·2%).

(d) *With ethereal hydrochloric acid.* Ethereal hydrochloric acid (2 mol.) was added with swirling to a solution of the complex (II) (0·970 g., 1 mol.) in chloroform (30 ml.). The pale yellow *product* separated immediately (Found: C, 30·65; H, 3·5; N, 5·45. $C_{13}H_{17}Cl_3N_2Pt$ requires C, 31·05; H, 3·4; N, 5·55%). It has a molecular conductivity of 5·7 ohm^{-1} $cm.^2$ at 20° in $3·3 \times 10^{-3}$M-nitrobenzene solution.

(e) *Isomerisation in benzene.* A solution of the complex (II) in benzene was heated under reflux for 5—10 min. and the solvent removed under reduced pressure. This yielded compound (VII) as a bright yellow solid, m. p. 160—165° (decomp.) (Found: C, 33·05; H, 3·55; N, 5·95%). The preparation was repeated several times, but, although the elemental analyses were satisfactory, the m. p. and infrared spectrum of the product were not reproducible, even after repeated recrystallisation from chloroform–light petroleum (b. p. 60—80°) and chromatographic treatment on alumina.

To identify the gases evolved in the reactions of compounds (I) and (II) with the tertiary phosphines, sodium iodide, and potassium cyanide, these reactions were repeated *in vacuo* in a small reaction vessel connected to a 5 cm. infrared gas cell. The gases evolved on thermal decomposition of complexes (I), (II), and (VII) were collected similarly and analysed by examination of their infrared spectra.

Infrared spectra were recorded on a Grubb–Parsons GS2A spectrometer. Solids were examined as mulls in "Nujol" and hexachlorobutadiene.

The magnetic resonances of the hydrogen nuclei were obtained at 40 Mc. with a Varian Associates 4300 B spectrometer, with flux stabilisation and sample spinning. The spectra were obtained for solution in chloroform; the positions of the peaks were measured by using sidebands generated by a Muirhead Decade oscillator.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
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150. *The Nuclear Magnetic Resonance Spectrum of* cis-1,2-*Difluoroethylene.*

By T. D. Coyle, S. L. Stafford, and F. G. A. Stone.

1,2-Difluoroethylene was obtained as one of the products of the reaction between diborane and tetrafluoroethylene [1] and by a more classical route.[2] In both cases the product was formulated as a "*cis–trans*"-mixture. We have now determined that both reactions yield predominantly (if not only) *cis*-isomer. The molecule is a simple example of an A_2X_2 nuclear-spin system, and analysis of the nuclear magnetic resonance spectrum reveals features which are of interest in the light of recent studies of other fluoro-olefins [3] and current interest in nuclear-spin coupling effects.

Vapour-phase chromatography, through several different columns, revealed only one component in a sample of 1,2-difluoroethylene from the diborane reaction. Isomeric purity was confirmed by ^{19}F and ^{1}H nuclear magnetic resonance measurements, which yielded identical ten-line spectra of the kind expected for a single A_2X_2 species. The general character of the infrared spectrum, especially the presence of a moderately intense band at 1730 cm.$^{-1}$ in the carbon–carbon double-bond stretching region, showed that the single isomer present is in fact the *cis*-compound. The infrared spectrum reported by Haszeldine and Steele [2] for what was also presumed to be a *cis–trans*-mixture agrees completely with the spectrum of our compound, indicating that their material is also the *cis*-isomer.

The relative stabilities of the two isomers are unknown. However, in the analogous 1,2-dichloroethylenes the *cis*-form is the more stable.[4] Appearance of only one isomer in the products of the diborane–tetrafluoroethylene reaction and of the dehalogenation may thus be due to thermodynamic factors and may not reflect any geometric specificity in the formation of the difluoroethylene.

The ^{19}F and ^{1}H nuclear magnetic resonance spectra are identical, consisting of ten lines disposed centrosymmetrically at 17·6, 18·9, 35·5, 38·2, and 46·0 c./sec. relative to the centre. The proton system is centered at $-6{\cdot}2_0$ p.p.m. (hexamethyldisiloxane internal reference) and the fluorine system at $167{\cdot}_7$ p.p.m. (trichlorofluoromethane external reference).

An analysis of the nuclear magnetic resonance spectrum for the general A_2X_2 case has been applied to 1,1-difluoroethylene.[5] It has been pointed out that the analysis does not yield the signs of the coupling constants, and that J_{HH} cannot be distinguished from J_{FF}, nor J_{HF} (*trans*) from J_{HF} (*gem*). However, reasonable assignments can be made by comparison with coupling constants in other molecules. The following assignments reproduce the observed line separations and yield calculated intensities in satisfactory agreement with the observed values: J_{HH} $2{\cdot}_0$ c./sec., J_{FF} $18{\cdot}_6$ c./sec., J_{HF} (*trans*) $20{\cdot}_1$ c./sec., J_{HF} (*gem*) $71{\cdot}_9$ c./sec.

The values of J_{HH} and J_{FF} are significantly lower than those found previously for similar molecules,[6] thus extending the range of "characteristic" spin coupling constants in fluoroethylenes. It is of interest that an unusually low coupling constant has also been reported between *cis*-protons for 1,2-dichloroethylene.[7]

Experimental.—cis-1,2-*Difluoroethylene.* The material used in this work was a sample from the original preparation of the compound in this laboratory,[1] repurified by fractional

[1] Bartocha, Graham, and Stone, *J. Inorg. Nuclear Chem.*, 1958, **6**, 119.
[2] Haszeldine and Steele, *J.*, 1957, 2800.
[3] McConnell, Reilly, and McLean, *J. Chem. Phys.*, 1956, **24**, 479.
[4] Wood and Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 1650.
[5] McConnell, Reilly, and McLean, *J. Chem. Phys.*, 1955, **23**, 1152.
[6] See Pople, Schneider, and Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, and references cited therein.
[7] Cohen, Sheppard, and Turner, *Proc. Chem. Soc.*, 1958, 118.

XUM

condensation in the vacuum-system. The infrared spectrum showed that the compound was not affected by prolonged storage in the vapour phase at room temperature.

Apparatus and instruments. A Perkin–Elmer vapour fractometer was used for the attempted separation into geometrical isomers. The instrument contained thermistor detectors, and used helium gas as carrier. Columns investigated were " di-isododecyl phthalate " on crushed firebrick (6 ft. and 12 ft. in length), activated charcoal (6 ft.), dimethylnaphthalene on crushed firebrick (6 ft.), and silver nitrate–glycerol on crushed firebrick (6 ft. and 12 ft.). Infrared spectra of the vapour were recorded with a Perkin–Elmer model 21 recording spectrometer equipped with a sodium chloride prism. Nuclear magnetic resonance spectra were measured with a Varian V4300B spectrometer equipped with superstabiliser. ^{19}F measurements were made at 40 Mc./sec., ^{1}H measurements at 40 and 60 Mc./sec. The samples, pure liquid with trichlorofluoromethane as an external reference and a 10% solution in carbon tetrachloride with hexamethyldisiloxane added (*ca.* 1%) as an internal reference, were contained in Pyrex sample tubes of 5 mm. outside diameter, sealed under a vacuum. A precision audio-oscillator and associated frequency counter were used for measurements of line separations.

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151. *Nitroethylene and Some Indolylmagnesium Iodides.*

By R. M. Acheson and A. R. Hands.

A number of indoles[1,2] are known to react directly with nitroethylene, yielding the corresponding 3-2′-nitroethylindoles, and it is stated[1] that indolylmagnesium iodide gives a better yield of 3-2′-nitroethylindole than indole itself. The reaction of nitroethylene with three indolylmagnesium iodides was therefore examined, as the products were needed in another connexion.

5,6-Dimethoxy-1-indolylmagnesium iodide with nitroethylene gave the corresponding 3-2′-nitroethylindole derivative, as proved by reduction to 5,6-dimethoxytryptamine which was compared, as the picrate, with a specimen prepared by another method.[3] 3-Methyl-1-indolyl- and 5-benzyloxy-1-indolyl-magnesium iodide gave 3-methyl-1-2′-nitroethylindole and 5-benzyloxy-1,3-di-2′-nitroethylindole respectively. The isomeric indolenine structures for these adducts are excluded by their insolubility in acid and by their ultraviolet absorption spectra.

Experimental.—Deactivated alumina was prepared by shaking alumina (Spence, grade " H," 2 kg.) with acetic acid (10 ml.) and water (90 ml.). Nitroethylene, b. p. 40—45°/90 mm., was prepared by Buckley and Scaife's method.[4] 5-Benzyloxyindole-2-carboxylic acid was prepared by Boehme's method;[5] it gave 5-benzyloxyindole on decarboxylation,[6] b. p. 200—210°/0·1 mm., m. p. 104° (from ether). 5,6-Dimethoxyindole was obtained by the method of Huebner, Troxell, and Schroeder,[3] and had m. p. 156° after chromatography on deactivated alumina with benzene as the eluent. The ultraviolet absorption spectra were measured for MeOH solutions, and the infrared spectra for Nujol mulls.

3-Methyl-1-2′-nitroethylindole. 3-Methyl-1-indolylmagnesium iodide was prepared by Baker's method[7] from magnesium (0·86 g.), ethyl iodide (5·61 g.), and skatole (4·72 g.) in ether (30 ml.). The solution was stirred and cooled in an ice-bath, and nitroethylene (2·63 g.) in ether

[1] Noland and Hartman, *J. Amer. Chem. Soc.*, 1954, **76**, 3227.
[2] Lange, *Diss. Abs.*, 1959, **20**, 1172; Noland and Horden, *J. Org. Chem.*, 1959, **24**, 894.
[3] Huebner, Troxell, and Schroeder, *J. Amer. Chem. Soc.*, 1953, **75**, 5887.
[4] Buckley and Scaife, *J.*, 1947, 1471.
[5] Boehme, *J. Amer. Chem. Soc.*, 1953, **75**, 2502.
[6] Stoll, Troxler, Peyer, and Hoffman, *Helv. Chim. Acta*, 1955, **38**, 1452.
[7] Baker, *J.*, 1946, 461.

(20 ml.) was added dropwise during 15 min. A yellow solid separated. The mixture was stirred for 1 hr. at room temperature, and was then refluxed for 1 hr.; the solid became brown and some brown fumes were evolved. After cooling to 0° the mixture was added with stirring to acetic acid (30 ml.) and water (100 ml.). The aqueous layer was separated, and was basified with an excess of solid sodium carbonate. The ether layer was shaken with a saturated solution of sodium carbonate until gas evolution ceased. The original aqueous layer and the sodium carbonate washings were extracted with ether, and the extracts were added to the original washed ether layer. The combined ether solutions were washed with water, dried ($MgSO_4$), and evaporated on the water-bath. The dark brown, tarry residue was chromatographed on deactivated alumina (250 g.) from benzene. The first eluate (600 ml.) yielded skatole (0·78 g., 17%), m. p. 95°. The second (500 ml.) gave *3-methyl-1-2′-nitroethylindole* (0·06 g., 8%), pale yellow prisms (from ether), m. p. 85° (Found: C, 64·4; H, 5·7; N, 13·8. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%), $\nu_{max.}$ 1520 and 1340 cm.$^{-1}$ (NO_2), $\lambda_{max.}$ 224, 277, 285, and 295 (infl.) mμ (log ε 4·77, 3·98, 3·99, 3·91). The *picrate* separated from ethanol as dark red needles with a bronze reflex, m. p. 105° (Found: C, 46·6; H, 3·4; N, 16·1. $C_{17}H_{15}N_5O_8$ requires C, 47·1; H, 3·5; N, 16·2%). Further elution with ether (2·5 l.) gave a brown oil (1·16 g.).

1-2′-Aminoethyl-3-methylindole. 3-Methyl-1-2′-nitroethylindole (1·0 g.) in absolute ethanol (150 ml.) and 5% palladised charcoal (1·0 g.) was shaken for 2 hr. under hydrogen at 2 atm. Distillation of the filtrate gave *1-2′-aminoethyl-3-methylindole* (0·66 g., 77%), b. p. 130—133° (bath)/0·3 mm., as a colourless oil, $n_D^{15·5}$ 1·6010, rapidly darkening in the air (Found: C, 75·8; H, 7·9; N, 15·6. $C_{11}H_{14}N_2$ requires C, 75·8; H, 8·1; N, 16·1%). The *picrate* formed scarlet prisms (from ethanol), m. p. 222° (decomp.) (Found: C, 51·0; H, 4·3; N, 17·6. $C_{17}H_{17}N_5O_7$ requires C, 50·6; H, 4·3; N, 17·4%).

5-Benzyloxy-1,3-di-2′-nitroethylindole. Nitroethylene (3·65 g.) in ether (20 ml.) was added dropwise to a stirred ice-cooled suspension of 5-benzyloxy-1-indolylmagnesium iodide, prepared from 5-benzyloxyindole (11·15 g.), ethyl iodide (7·80 g.), and magnesium (1·20 g.) in ether (100 ml.). The mixture was stirred at room temperature for 1 hr., refluxed for 1 hr., cooled for 1 hr., and poured with stirring into acetic acid (50 ml.) and water (150 ml.). The mixture was worked up as for 3-methyl-1-2′-nitroethylindole, and the tarry product was chromatographed on deactivated alumina (250 g.). Elution with benzene (2 l.) gave 5-benzyloxyindole (5·83 g., 52%), m. p. 103—104°. Further elution with ether (500 ml.) gave *5-benzyloxy-1,3-di-2′-nitroethylindole* (0·43 g., 2·3%), which crystallised from ethanol in needles, m. p. 153° (Found: C, 62·0; H, 5·3; N, 11·5. $C_{19}H_{19}N_3O_5$ requires C, 61·8; H, 5·2; N, 11·4%), $\nu_{max.}$ 1560 and 1377 cm.$^{-1}$ (NO_2), $\lambda_{max.}$ 220, 276, 302, 312 (infl.) mμ (log ε 4·55, 3·91, 3·74, 3·66). Further elution with ether (500 ml.) gave a brown oil (0·19 g.).

5,6-Dimethoxy-3,2′-nitroethylindole. 5,6-Dimethoxy-1-indolylmagnesium iodide, obtained from 5,6-dimethoxyindole (10·27 g.), ethyl iodide (9·05 g.), and magnesium (1·39 g.) in ether (100 ml.), was stirred and cooled in an ice-bath during the addition of a solution of nitroethylene (4·23 g.) in ether (50 ml.). The mixture was worked up as in the previous preparation, and the tarry product was chromatographed on deactivated alumina (250 g.). Elution with benzene–ether (9 : 1 v/v; 4·5 l.) gave 5,6-dimethoxyindole (3·43 g., 33%), m. p. 156°. Elution with ether (500 ml.) then gave a material of m. p. 129—146° (0·34 g.). Further elution with ether (1·5 l.) gave 5,6-dimethoxy-3-2′-nitroethylindole (1·42 g., 10%), orange prisms (from benzene), m. p. 133° (Found: C, 57·9; H, 5·4; N, 11·1. $C_{12}H_{14}N_2O_4$ requires C, 57·6; H, 5·6; N, 11·2%), $\nu_{max.}$ 3290 (NH), and 1537 and 1370 cm.$^{-1}$ (NO_2), $\lambda_{max.}$ 220, 279 (infl.), 296, 301, and 306 (infl.) mμ (log ε 4·50, 3·75, 3·94, 3·92). The *picrate* separated from ethanol as purple needles with a bronze reflex, m. p. 127—128° (decomp.) (Found: C, 45·5; H, 3·7; N, 14·5. $C_{18}H_{17}N_5O_{11}$ requires C, 45·1; H, 3·6; N, 14·6%). Further elution with ether (2 l.) gave an oil (0·73 g.).

5,6-Dimethoxytryptamine. 5,6-Dimethoxy-3-2′-nitroethylindole (0·3 g.), 5% palladised charcoal (0·3 g.), and ethanol (100 ml.) were shaken for 1 hr. under hydrogen at 5 atm. Filtration and distillation at 190—200° (bath)/0·05 mm. gave a colourless oil (0·19 g., 72%) which was identified as 5,6-dimethoxytryptamine by conversion into the picrate, m. p. and mixed m. p. 223—224° (decomp.). The infrared absorption spectra of the two specimens were identical.

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XUM

152. 5-*Hydroxyskatole.*

By R. M. Acheson and A. R. Hands.

5-Hydroxyskatole, m. p. 116°, required for chromatographic studies, has been synthesised for the first time by a structurally unequivocal route, by hydrogenation of 5-benzyloxygramine over platinum. The reduction of 5-benzyloxygramine to 5-benzyloxyskatole by zinc dust and sodium hydroxide, a procedure used earlier [1] for the conversion of gramine into skatole, followed by hydrogenolysis of the 5-benzyloxyskatole, was much less satisfactory. A compound described as 5-hydroxyskatole, m. p. 108—109°, has been obtained [2] from 2,3-dihydroskatole and potassium nitrosodisulphonate, but no analytical data or structure proof was given.

Experimental.—*5-Hydroxyskatole.* (i) 5-Benzyloxygramine (0·50 g.), Adams platinum catalyst (0·30 g.), and methanol (50 ml.) were shaken for 5 hr. under hydrogen at 5 atm. Filtration, evaporation, and recrystallisation of the residue from 1 : 3 v/v ether–light petroleum (b. p. 40—60°) gave *5-hydroxyskatole* (0·19 g., 72%), m. p. 116° (Found: C, 73·1; H, 5·7; N, 9·8. C_9H_9NO requires C, 73·4; H, 6·2; N, 9·5%). (ii) 5-Benzyloxyskatole (100 mg.), 5% palladised charcoal (100 mg.), and ethanol (30 ml.) were shaken for 24 hr. under hydrogen at 5 atm. Filtration and evaporation of the filtrate gave a tarry residue, which on 3 recrystallisations from ether–light petroleum (as above) gave 5-hydroxyskatole (8 mg., 13%), m. p. and mixed m. p. 116°, 115—116°.

5-Benzyloxyskatole. Sodium hydroxide (2·0 g.) in water (16 ml.) was added to 5-benzyloxygramine (1·37 g.) in methanol (26 ml.), and the mixture was heated to boiling. Zinc dust (1·6 g.) was added during 2 hr. with stirring. Heating and stirring were continued for 12 hr., an oily lower layer separating. Methanol was removed on the water-bath, and the cooled residue was extracted with ether (3 × 100 ml.). The extracts were dried (Na_2SO_4) and on evaporation gave an oil, which was chromatographed from benzene on alumina (150 g.) deactivated by acetic acid (0·75 ml.) and water (6·7 ml.). The first eluate (250 ml.) gave an oil (10 mg.); further elution (250 ml.) gave *5-benzyloxyskatole* (0·76 g., 64%), crystallising from light petroleum (b. p. 40—60°) in white needles, m. p. 118° (Found: C, 81·0; H, 6·3; N, 5·7. $C_{16}H_{15}NO$ requires C, 81·0; H, 6·4; N, 5·9%). The *picrate* separated from methanol as crimson needles with a bronze reflex, m. p. 164° (Found: C, 57·0; H, 3·8; N, 11·8. $C_{22}H_{18}N_4O_8$ requires C, 56·7; H, 3·9; N, 12·0%). Further elution with benzene (2 l.) gave a resin (0·33 g.).

We thank the Mental Health Research Fund for a Grant for the provision of scientific assistance.

Department of Biochemistry, University of Oxford. [*Received, July 25th,* 1960.]

[1] Terent'ev, Dzbanovskii, and Favorskaya, *Zhur. obshchei Khim.*, 1953, **23**, 2035.
[2] Teuber and Staiger, *Chem. Ber.*, 1956, **89**, 489.

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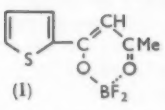
153. *So-called "2-Triacetylthiophen": (a Boron Compound).*

By G. M. Badger and Jenneth M. Sasse.

Acetylation of 2-acetylthiophen with acetic anhydride and boron trifluoride has been reported [1] to give a compound which (on the basis of a sulphur analysis and the fact that it gave thiophen-2-carboxylic acid on oxidation) was named "2-triacetylthiophen."



(I)

The preparation of this compound has been repeated, and it has been identified as 3-oxo-1-2′-thienylbut-1-enyloxyboron difluoride (I) by more complete analysis and by comparison with a specimen prepared by treatment of 1-2′-thienylbutane-1,3-dione [2] with boron trifluoride. Several other examples of boron difluoride complexes with β-diketones have been reported.[3]

[1] Hartough and Kosak, *J. Amer. Chem. Soc.*, 1948, **70**, 867.
[2] Harris and Levine, *J. Amer. Chem. Soc.*, 1948, **70**, 3360.
[3] Morgan and Tunstall, *J.*, 1924, **125**, 1963; Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635; Hauser, Frostick, and Man, *ibid.*, 1952, **74**, 3231; McOmie and Tute, *J.*, 1938, 3226.

Experimental.—*1-2′-Thienylbutane-1,3-dione.* Harris and Levine's method [2] was followed, except that after the decomposition of the copper salt, the ether extract was evaporated and the residue extracted with light petroleum (b. p. 40—60°). The extract gave yellow plates, m. p. 34°. The copper salt formed green needles, m. p. 232—234° (lit.,[2] m. p. 228—230°).

3-Oxo-1,2′-thienylbut-1-enyloxyboron difluoride. (i) Hartough and Kosak's method [1] was followed, except that the boron trifluoride–acetic acid complex was used instead of boron trifluoride–ether complex (half-scale; yield 8 g.; m. p. 172°). The analytical sample, after sublimation and recrystallisation from benzene, had m. p. 174—175° (lit.,[1] m. p. 176—177°) and this *product* gave a positive qualitative test for boron (Found: C, 44·4; H, 3·5; S, 14·7; F, 17·1. $C_8H_7BF_2O_2S$ requires C, 44·5; H, 3·3; S, 14·9; F, 17·6%) (previous analysis [1]: Found, S, 14·9. $C_{10}H_{10}O_3S$ requires C, 57·2; H, 4·8; S, 15·3%).

(ii) 1-2′-Thienylbutane-1,3-dione (134 mg.) was dissolved in glacial acetic acid (2 c.c.), a 40% solution (1 ml.) of boron trifluoride in acetic acid was added, and the mixture shaken. A yellow precipitate appeared almost immediately, but the mixture was set aside for ½ hr. The solid was collected, and a further quantity was isolated after treatment of the mother-liquor with dilute sodium acetate solution. The product crystallised from benzene as orange-yellow needles of the difluoride (125 mg., 73%), m. p. and mixed m. p. 174—175°. The infrared spectra of the two samples were superimposable.

We thank Mr. A. G. Moritz for the infrared spectra. Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

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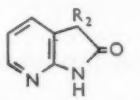
154. 2,3-*Dihydro*-3,3-*dimethyl*-1H-1,7-*diazaindan*-2-*one*.

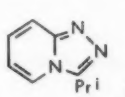
By G. E. FICKEN and J. D. KENDALL.

ALTHOUGH oxindoles have been very thoroughly examined,[1] very little is known of their aza-analogues in which the six-membered ring is pyridine instead of benzene: the only reported preparation of such a compound is of 2,3-dihydro-1,7-diazaindan-2-one [2] (I; R = H) (2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-2-one).

We have found that a compound which appears to be 2,3-dihydro-3,3-dimethyl-1*H*-1,7-diazaindan-2-one (I; R = Me) is obtained in small yield by heating *N*-isobutyryl-*N*′-2-pyridylhydrazine with calcium oxide, analogously to the Brunner oxindole synthesis.[3] The infrared spectrum of the compound is consistent with an azaoxindole formulation.



(I)



(II)

The low yield can be ascribed partly to the weak susceptibility of the pyridine ring to electrophilic substitution, and partly to the formation of the pyridotriazole (II). Although the latter was not isolated in the present reaction, it is formed when the isobutyrylhydrazine is heated alone at 250°.

We have been unable to prepare azaoxindoles by the use of the oxindole syntheses of Stollé [4] (2-α-bromo-*N*-methylisobutyramidopyridine heated with aluminium chloride) or of Hinsberg [5] (2-methylaminopyridine treated with glyoxal sodium bisulphite).

Experimental.—N-*Isobutyryl*-N′-*2-pyridylhydrazine.* This *compound* was prepared in 44% yield from isobutyric anhydride and 2-hydrazinopyridine, according to the directions for

[1] Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, 1952, Vol. III, pp. 126—186.
[2] Kägi, *Helv. Chim. Acta*, 1941, **24**, 141E.
[3] Brunner, *Monatsh.*, 1906, **27**, 1183.
[4] Stollé, *Ber.*, 1914, **47**, 2120.
[5] Hinsberg and Rosenzweig, *Ber.*, 1894, **27**, 3253.

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the acetylation of the hydrazine.[6] It formed plates, m. p. 135—137°, from benzene (Found: C, 60·2; H, 7·0. $C_9H_{13}N_3O$ requires C, 60·3; H, 7·3%).

2,3-*Dihydro*-3,3-*dimethyl*-1H-1,7-*diazaindan*-2-*one*. The above hydrazine (10 g.) and freshly ignited calcium oxide (20 g.) were mixed and heated in a nitrogen stream at 290—300°; slow evolution of ammonia occurred. After 2 hr. the mixture was cooled and dissolved in concentrated hydrochloric acid and the solution was extracted with chloroform continuously for 24 hr. The residual aqueous solution was treated with excess of ammonia, saturated with ammonium chloride, and, after filtration, continuously extracted with chloroform. The extracts were evaporated to leave a brown oil which was treated in ethanol with excess of ethanolic picric acid. Recrystallisation from ethanol and then ethyl acetate (twice) gave the *diazaindanone picrate* (0·74 g.), yellow plates, m. p. 231—232° (Found: C, 46·1, 46·4; H, 3·1, 3·5; N, 17·55. $C_{15}H_{13}N_5O_8$ requires C, 46·0; H, 3·35; N, 17·9%). The picrate was stirred with 0·5N-sodium hydroxide (50 ml.) until a homogeneous solution was obtained. Continuous extraction with chloroform and evaporation of the extract yielded a solid (0·29 g.) which after two crystallisations from ethyl acetate gave 2,3-*dihydro*-3,3-*dimethyl*-1H-1,7-*diazaindan*-2-*one*, colourless plates, m. p. 178—179° (Found: 67·2; H, 6·4; N, 17·6. $C_9H_{10}N_2O$ requires C, 66·65; H, 6·2; N, 17·3%). The infrared spectrum (Nujol mull) showed bands at 3100m (NH stretch), 1940w, 1720s (C=O stretch), 1610s (NH bend), 1442w, 1430m, 1410m, 1358w, 1328m, 1300w, 1278w, 1258w, 1236m, 1200s, 1154s, 1120m, 1086m, 1056w, 1038m, 1016w, 978w, 948m, 903w, 820m, 800m, 781s (CH out-of-plane, 3 adjacent H) cm.$^{-1}$.

3-*Isopropyl*-1,2,3a-*triazaindene* (II). *N*-Isobutyryl-*N'*-2-pyridylhydrazine (9·1 g.) was heated at 250° for 30 min., water being evolved. Distillation of the residue gave 3-*isopropyl*-1,2,3a-*triazaindene* (7·9 g.), b. p. 144°/0·2 mm., m. p. 44° (Found: C, 66·9; H, 6·8. $C_9H_{11}N_3$ requires C, 67·0; H, 6·9%). The *picrate*, yellow needles from methanol, had m. p. 201° (Found: C, 46·2; H, 3·5; N, 21·3. $C_{15}H_{14}N_6O_7$ requires C, 46·2; H, 3·6; N, 21·5%). The infrared spectrum of the base (supercooled liquid) had bands at 3450w, 3110w, 3000m (CH stretch), 1680w, 1645m (C=C or C=N stretch), 1580w, 1535w, 1515s, 1464m, 1392m, 1372m, 1344 (last 3 CH bend), 1296w, 1274m, 1186w, 1142w, 1102w, 1060m, 1042m, 1000w, 926w, 888w, 837w, 779w, 764s, 749s, 714m, 690m cm.$^{-1}$.

We thank Mr. L. R. Brooker for the infrared spectra measurements, and for valuable discussions on their interpretation, also Miss J. Connor for the microanalyses.

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[*Received, July 12th,* 1960.]

[6] Fargher and Furness, *J.*, 1915, **107**, 688.

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155. 2,4'-*Diphenylbiphenyl* [op'-*Quaterphenyl*].

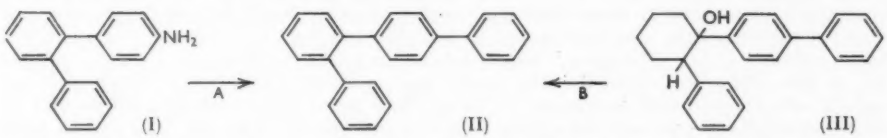
By D. H. HEY, M. J. PERKINS, and GARETH H. WILLIAMS.

THE preparation of 2,4'-diphenylbiphenyl (*op'*-quaterphenyl) has been reported by Dale,[1] who obtained it by means of an Ullmann reaction between 2- and 4-iodobiphenyl and recorded m. p. 117·5—118°. More recently Wiley and Wakefield [2] reported its preparation by tetrazotisation of 2,4'-diaminobiphenyl and decomposition of the derived tetrazonium hydroxide in the presence of benzene; they obtained the same compound from the decomposition of 2,4'-di(acetylnitrosoamino)biphenyl in benzene and recorded m. p. 209—210°. We required an authentic specimen of this hydrocarbon for reference purposes and have obtained it by two new and unambiguous routes. Our product has properties in agreement with those reported by Dale [1] but different from those reported by Wiley and Wakefield.[2]

o-Terphenyl was nitrated in the 4-position,[3] and the nitro-compound was reduced to

[1] Dale, *Acta Chem. Scand.*, 1957, **11**, 640, 650.
[2] Wiley and Wakefield, *J. Org. Chem.*, 1960, **25**, 132.
[3] Allen and Burness, *J. Org. Chem.*, 1949, **14**, 175.

4-amino-*o*-terphenyl [3] (I), acetylated, and nitrosated. The resulting 4-(acetylnitrosoamino)-*o*-terphenyl was allowed to decompose in benzene solution, and gave 2,4′-diphenylbiphenyl (II), m. p. 120—120·5° (method A). In the second synthesis the secondary alcohol



(I) (II) (III)

(III) from the reaction of 2-phenylcyclohexanone [4] with 4-biphenylylmagnesium bromide was dehydrated and dehydrogenated to yield 2,4′-diphenylbiphenyl (II), m. p. 119—120° (method B). The melting point of this specimen (119—120°) was not depressed on admixture with the sample prepared by method A.

Experimental.—M. p.s are corrected.

Method A. *o*-Terphenyl was nitrated by Allen and Burness's method,[3] to give 4-nitro-*o*-terphenyl, m. p. 110—114° (lit.,[3] 116°), which was reduced with tin and hydrochloric acid to the corresponding amino-compound, m. p. 117·5—118·5° (lit.,[3] 117—118°). The benzoyl derivative of this amine after crystallisation from aqueous methanol had m. p. 187—188° (lit.,[5] 175°) (Found: C, 85·9; H, 5·45. Calc. for $C_{25}H_{19}NO$: C, 86·0; H, 5·45%). 4-Amino-*o*-terphenyl (4·05 g.) was treated with acetyl chloride in pyridine to give *4-acetamido-o-terphenyl* (4·34 g.) in needles, m. p. 159·5—160·5° (from aqueous methanol) (Found: C, 84·0; H, 6·1. $C_{20}H_{17}NO$ requires C, 83·75; H, 6·0%). Nitrosyl chloride (1·5 g.) in acetic anhydride (10 ml.) was added, slowly and with stirring, to a solution of this acetyl derivative (4·0 g.) in glacial acetic acid (25 ml.) and acetic anhydride (15 ml.) at 0° containing phosphorus pentoxide (0·5 g.), and fused sodium acetate (4 g.). The solution was stirred for 15 min. and then poured into stirred ice-water (500 ml.). The mixture was stirred at 0° for 1 hr., and the yellow precipitate filtered off. This *N*-nitroso-derivative decomposed suddenly at about 90°, without melting. The entire product was stirred with cooled "AnalaR" benzene (150 ml.) and anhydrous magnesium sulphate (20 g.), while the temperature was allowed to rise to 20°. Stirring was continued for 48 hr., after which the solution was boiled for 10 min., filtered, and then washed with successive portions of concentrated sulphuric acid until both layers were almost colourless. The organic layer was washed with aqueous sodium hydrogen carbonate, and water (twice), and dried ($MgSO_4$). The solvent was distilled off, and the residue chromatographed on alumina, which was then eluted with 3 : 1 light petroleum (b. p. 40—60°)–benzene. Evaporation of the early fractions of the eluate left a solid (1·53 g.), which was crystallised to constant m. p. (120—120·5°) from light petroleum (b. p. 40—60°) (Found: C, 94·0; H, 5·9. Calc. for $C_{24}H_{18}$: C, 94·1; H, 5·9%). The infrared absorption spectrum of the product in a Nujol mull agreed with that reported by Dale.[1] The ultraviolet absorption in ethanol showed maxima at 249 mμ (ε 2·72 × 10^4) and 277 mμ (ε 2·33 × 10^4). Dale [1] reported m. p. 117·5—118°, $\lambda_{max.}$ (in hexane) 248 mμ (ε 2·72 × 10^4), 276 mμ (ε 2·31 × 10^4).

Method B. 4-Bromobiphenyl (9 g.) was treated with magnesium (1 g.) in tetrahydrofuran (12 ml.) under nitrogen. After the initial reaction had subsided, the solution was boiled under reflux for ½ hr. 2-Phenylcyclohexanone, prepared by Newman and Farbman's method,[4] m. p. 60—61° (lit.,[6] 61°) [from light petroleum (b. p. 40—60°)] (Found: C, 82·7; H, 8·1. Calc. for $C_{12}H_{14}O$: C, 82·7; H, 8·1%) (6 g.), in tetrahydrofuran (12 ml.) was added slowly to the Grignard reagent, and the mixture was refluxed under nitrogen for 3 hr. The resulting solution was treated with excess of N-hydrochloric acid and extracted with benzene (2 × 20 ml.). The benzene extract was dried ($MgSO_4$), and the solvent removed under reduced pressure to give an oil, which was boiled under reflux, with stirring, for 5 hr. with 85% formic acid (20 ml.). The resulting solution was cooled and added to water (150 ml.); a white solid separated, which, after crystallisation from a minimum of ethanol, had m. p. 100—120° (7 g.). Crystallisation to constant m. p. from ethanol gave a compound A in colourless needles, m. p. 135—136°. Concentration of the mother-liquors from these crystallisations gave a solid melting in the

[4] Newman and Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1550.
[5] Allen and Pingert, *J. Amer. Chem. Soc.*, 1942, **64**, 2639.
[6] Levy and Sfiras, *Bull. Soc. chim. France*, 1931, **49**, 1830.

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range 90—115°, but further concentration gave a minor product B as prisms which crystallised to constant m. p. (101·5—102·5°) from ethanol. Both compounds analysed correctly for a phenylbiphenylylcyclohexene, and further separation was not attempted (Found, for A: C, 92·8; H, 7·25. For B: C, 92·8; H, 7·1. Calc. for $C_{24}H_{22}$: C, 92·85; H, 7·15%). The two compounds are probably isomers differing in the position of the double bond in the non-aromatic ring. A solution of the mixed product (5 g.) and chloranil (7 g.) in xylene (35 ml.) was boiled under reflux for 16 hr. The solution was cooled and the solid tetrachloroquinol which separated (m. p. 234—238°) was removed. The filtrate was combined with benzene washings of the quinol, and extracted with 2N-sodium hydroxide (three times), water, and repeatedly with concentrated sulphuric acid until the organic layer was pale yellow. This was then washed again with water, aqueous sodium hydroxide (twice, with filtration to remove a trace of solid), and finally with water (twice). The solution was then dried ($MgSO_4$), and the solvent distilled off at reduced pressure, leaving a brown oil. This was dissolved in light petroleum (b. p. 40—60°) (50 ml.) and cooled at 0° overnight. Clusters of crystals tinged with red separated together with a powdery precipitate which was removed by decantation and discarded. The crystals had m. p. 116—119°, alone and on admixture with 2,4′-diphenylbiphenyl prepared by method A, and showed an identical infrared absorption spectrum. Further recovery of the compound from the mother-liquors gave a total yield of 2·4 g. Treatment with charcoal in methanol raised the m. p. to 119—120°, but did not completely remove the red colour (Found: C, 94·2; H, 5·75. Calc. for $C_{24}H_{18}$: C, 94·1; H, 5·9%).

Thanks are accorded to the Department of Scientific and Industrial Research for the award of a Studentship to M. J. P.

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156. *Molybdenum*(II) *Complexes containing Triphenyl-phosphine Oxide or -arsine Oxide*

By J. C. SHELDON.

THE oxides of triphenyl-phosphine and -arsine readily form two types of chloromolybdenum(II) complex (M = P or As): non-electrolytes, $[(Mo_6Cl_8)Cl_4(Ph_3MO)_2]$, and electrolytes, $[(Ph_3MO)_nH]_2[(Mo_6Cl_8)Cl_6]$. The non-electrolytes are probably octahedral complexes of the (Mo_6Cl_8) polynucleus and are non-hygroscopic and stable up to 200° *in vacuo*. Although these complexes dissociate in nitrobenzene solution, giving only half the required formula weight, they can be recovered unchanged from solution by addition of light petroleum. The M–O stretching frequencies appear at 1061 and 852 $cm.^{-1}$ in the phosphine oxide and the arsine oxide compound respectively, compared with 1185 and 879 $cm.^{-1}$ in the corresponding free oxide. This shift to lower frequencies is indicative of co-ordination *via* the M–O oxygen atom.

The electrolytes are derivatives of the acid $H_2[(Mo_6Cl_8)Cl_6]$, referred to as chloromolybdic(II) acid, and are listed in the Table along with their empirical formulæ, molar conductivities at 10^{-3}M, and cryoscopic molecular weights in nitrobenzene, and proposed structures. It is likely that chloromolybdic(II) acid is a strong acid in view of the size

Empirical formula	Proposed structure	Λ_m	M	Formula wt./M
$H_2[(Mo_6Cl_8)Cl_6],4Ph_3PO$	$[(Ph_3PO)_2H]_2[(Mo_6Cl_8)Cl_6]$	52	840	2·6
$H_2[(Mo_6Cl_8)Cl_6],6Ph_3PO$	$[(Ph_3PO)_2H]_2[(Mo_6Cl_8)Cl_6],2Ph_3PO$	49	650 *	4·2
$H_2[(Mo_6Cl_8)Cl_6],2Ph_3AsO$	$[Ph_3AsOH]_2[(Mo_6Cl_8)Cl_6]$	43	590 *	2·9
$H_2[(Mo_6Cl_8)Cl_6],4Ph_3AsO$	$[(Ph_3AsO)_2H]_2[(Mo_6Cl_8)Cl_6]$	43	810 *	2·9

* Recovered unchanged from solution.

and structure of the chloromolybdate(II) ion, and therefore the electrolytes are best regarded as chloromolybdate(II) salts. Thus it is convenient to formulate $H_2[(Mo_6Cl_8)Cl_6],2Ph_3AsO$ as a quaternary arsonium salt $[Ph_3As{\cdot}OH]_2[(Mo_6Cl_8)Cl_6]$.

However, a problem of formulation arises for the other chloromolybdate(II) salts in that they possess an oxide to proton ratio greater than 1. It is suggested that the cations in these salts are hydrogen-bonded complexes, *e.g.*, $[Ph_3P(As)OH\cdots OP(As)Ph_3]^+$, which may be related to the hydrogen dihalide ions, $[XHX]^-$, bv the oxygen atom of the $P(As)^+–O^-$ group behaving as a pseudohalide ion. The oxide to proton ratio found in these salts appears to be governed by that ratio in the preparative solutions, for the lower ratios are obtained from the stronger acid solutions. Furthermore, as arsine oxides are stronger bases than phosphine oxides,[1] the arsine oxide salt series tends to have lower oxide to proton ratios than the phosphine series. The proposed complex cations appear to be stable in nitrobenzene solution, as conductivity and molecular-weight studies show that the salts are 2 : 1 electrolytes. However, the compound $H_2[(Mo_6Cl_8)Cl_6],6Ph_3PO$ dissociates into more than 3 solute particles per molecule and it is necessary to formulate it as $[(Ph_3PO)_2H]_2[(Mo_6Cl_8)Cl_6],2Ph_3PO$. Salts of triphenyl-phosphine oxide,[2,3] and -arsine oxide [4] have been found previously, although there is only one report of oxide to proton ratios exceeding unity.[3]

The P(As)–O stretching bands undergo pronounced and complex changes when the oxides form chloromolybdate(II) salts. The P–O stretching band of the free oxide (1185 cm.$^{-1}$) is absent from the spectra of the phosphine oxide salts and the following bands are found in addition to the normal phosphine oxide absorption in the range 1250—770 cm.$^{-1}$: $H_2[(Mo_6Cl_8)Cl_6],4Ph_3PO$, 1149 (weak) and 955 (broad and strong); $H_2[(Mo_6Cl_8)Cl_6],6Ph_3PO$, 1132 (strong) and 1068 cm.$^{-1}$. In a like manner the As–O stretching band (879 cm.$^{-1}$) is absent from the spectra of the arsine oxide compounds, but the compound $H_2[(Mo_6Cl_8)Cl_6],2Ph_3AsO$ has additional bands at 872 (only moderately strong) and 770 cm.$^{-1}$ (strong), and the compound $H_2[(Mo_6Cl_8)Cl_6],4Ph_3AsO$ probably has an additional band almost coincident with a normal strong triphenylarsine oxide band at 740 cm.$^{-1}$.

Experimental.—Molar conductivities, cryoscopic molecular weights, and analyses were determined as previously described.[5] The infrared spectra were recorded by a Grubb-Parsons type GS2A double-beam grating spectrometer from Nujol mulls.

Triphenylphosphine oxide. The commercial material was adequate for preparative purposes and a resublimed sample had satisfactory m. p. and analysis.

Triphenylarsine oxide. The arsine oxide hydrate (obtained by treatment of triphenylarsine with aqueous hydrogen peroxide) proved suitable for the preparation of the complexes below. Vacuum-sublimed samples of the oxide hydrate analysed closely for the free arsine oxide and had melting ranges of 188—194° (lit.,[6] 190—191°) although they still showed some infrared absorption at 3380 and 1660 cm.$^{-1}$ characteristic of water.

General preparation of complexes. The non-electrolyte complexes, $[(Mo_6Cl_8)Cl_4(Ph_3MO)_2]$, may be obtained by heating the chloromolybdate(II) salts strongly *in vacuo* or, more conveniently, by mixing ethanolic solutions of the appropriate oxide and molybdenum(II) chloride and drying the precipitate *in vacuo*. The chloromolybdate(II) salts are precipitated or slowly crystallise from aqueous- or absolute-ethanolic solutions of the appropriate oxide and chloromolybdic(II) acid. The latter may be formed *in situ* from molybdenum(II) chloride, *i.e.*, Mo_6Cl_{12}, and 2 equiv. of hydrogen chloride. The particular salt obtained depends on the proportion of oxide to acid [both as chloromolybdic(II) acid and excess of hydrochloric acid] in the preparative solution; *e.g.*, the $4Ph_3AsO$ salt was given as an immediate precipitate on the addition of ethanolic chloromolybdic(II) acid to an excess of ethanolic arsine oxide, whereas the $6Ph_3PO$ salt separated slowly from an aqueous-ethanolic dilute hydrochloric acid solution of the phosphine oxide and chloromolybdic(II) acid. However, addition of excess of hydrochloric

[1] Nylén, *Z. anorg. Chem.*, 1941, **246**, 227.
[2] Michaelis and Soden, *Annalen*, 1885, **229**, 295.
[3] Pickard and Kenyon, *J.*, 1906, **89**, 262.
[4] La Coste and Michaelis, *Annalen*, 1880, **201**, 184; Michaelis, *ibid.*, 1902, **321**, 141; Steinkopf and Schwen, *Ber.*, 1921, **54**, 2791.
[5] Sheldon, *J.*, 1960, 1007.
[6] Jensen, *Z. anorg. Chem.*, 1943, **250**, 268.

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acid to these two preparations gave the $2Ph_3AsO$ and $4Ph_3PO$ salts respectively. Analyses are given below.

Tetrachlorobis[triphenylphosphine(or arsine) oxide]octa-μ_3-chlorohexamolybdenum(II). Found, for *phosphorus compound*: C, 26·8; H, 2·1; Cl, 27·7. $C_{36}H_{30}Cl_{12}Mo_6O_2P_2$ requires C, 27·8; H, 1·9; Cl, 27·4%. Found, for *arsenic compound*: C, 26·8; H, 2·0; As, 9·1; Cl, 25·9. $C_{36}H_{30}As_2Cl_{12}Mo_6O_2$ requires C, 26·3; H, 1·8; As, 9·1; Cl, 25·9%.

Bis{hydrogenbis[triphenylphosphine(or arsine)oxide]}hexachloro-octa-μ_3-chlorohexamolybdate(II). Found, for the *phosphine oxide salt*: C, 39·7; H, 3·0; Cl, 22·7; Mo_6Cl_8, 41; P, 5·65. $C_{72}H_{62}Cl_{14}Mo_6O_4P_4$ requires C, 39·4; H, 2·8; Cl, 22·7; Mo_6Cl_8, 39; P, 5·65%. Found for the *arsine oxide salt*: C, 35·9; H, 3·0; Cl, 21·2; Mo, 24·0. $C_{72}H_{62}As_4Cl_{14}Mo_6O_4$ requires C, 36·5; H, 2·6; Cl, 21·0; Mo, 24·4%.

Bis[hydrogenbis(triphenylphosphine oxide)]hexachloro-octa-μ_3-chlorohexamolybdate(II)-2-(*triphenylphosphine oxide*). Found: C, 47·4; H, 3·7; Cl, 18·2; Mo_6Cl_8, 32; P, 7·0. $C_{108}H_{92}Cl_{14}Mo_6O_6P_6$ requires C, 47·2; H, 3·35; Cl, 18·1; Mo_6Cl_8, 31; P, 6·8%.

Bis(hydroxotriphenylarsonium)hexachloro-octa-μ_3-chloro-hexamolybdate(II). Found: C, 25·4; H, 1·9; Cl, 28·8; Mo, 32·3. $C_{36}H_{32}As_2Cl_{14}Mo_6O_2$ requires C, 25·2; H, 1·85; Cl, 28·9; Mo, 33·6%.

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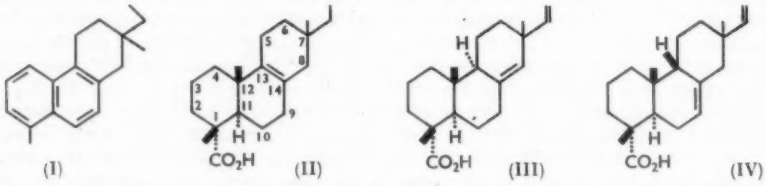
157. *Sandaraco- and Crypto-pimaric Acid.*

By J. W. APSIMON, B. GREEN, and W. B. WHALLEY.

OUR interest in diterpene acids has led us to examine the constitution of sandaraco- and crypto-pimaric acid.

Sandaracopimaric acid was originally isolated by Henry [1] and by Tschirch and Wolff.[2] Petru and Galik [3] recently demonstrated that this acid belongs to the pimaric acid series and claimed [4] that dehydrogenation of dihydrosandaracopimaric acid furnished the hydrocarbon (I), identical with that derived from dihydrodextropimaric acid.[5] They thus concluded that sandaraco- and dextro-pimaric acid had the same stereochemistry at $C_{(7)}$, but differed in the relative stereochemistry of the carboxyl groups at $C_{(1)}$.

In a re-examination of this problem we have isolated sandaracopimaric acid from a commercially available sandarac resin. The infrared absorption spectrum indicates the presence of a vinyl residue, which is readily saturated to furnish a dihydro-derivative ($\nu_{max.}$ 824 cm.$^{-1}$; >C=CH–). Dihydrosandaracopimaric acid is not isomerised by toluene-*p*-sulphonic acid in boiling benzene [6] but with hydrogen chloride in chloroform is converted into 7-allopimar-13(14)-en-15-oic acid [6] (II), thereby establishing that sandaraco- and isodextro-pimaric acid have the same configuration at positions 1, 7, 11, and 12.



We have previously shown [6] that dihydroisodextropimaric acid is isomerised to acid (II) by toluene-*p*-sulphonic acid in boiling benzene. Dihydropimaric acid is not isomerised under these conditions, from which it may be concluded that this reagent is specific for the

[1] Henry, *J.*, 1901, **79**, 1144.
[2] Tschirch and Wolff, *Archiv. Pharm.*, 1906, **244**, 684.
[3] Petru and Galik, *Coll. Czech. Chem. Comm.*, 1953, **18**, 717.
[4] Galik, Petru, and Kuthan, *Naturwiss.*, 1959, **46**, 322.
[5] Harris and Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 2081.
[6] Green, Harris, and Whalley, *J.*, 1958, 4715.

isomerisation of 13β-pimar-8(14)-enes [and probably of 13β-9(14)-enes] to pimar-13(14)-enes. Thus sandaracopimaric acid has a 13α-hydrogen. Since dihydrodextro- and dihydroisodextro-pimaric acid have plain rotatory dispersion curves which are positive and negative, respectively,[7] and dihydrosandaracopimaric acid has a plain, positive, rotatory dispersion curve, sandaracopimaric acid has the structure (III).*

A reputedly homogeneous diterpene acid, cryptopimaric acid, has been isolated from *Cryptomeria japonica* [8] and from *Dacrydium biforme* and *D. kirkii*,[9] and its identity with isodextropimaric acid has been proposed,[10,11,12] despite considerable variation [12] between the specific rotations of crypto- and isodextro-pimaric acid and their various, respective derivatives. On the other hand, Bruun, Ryhage, and Stenhagen [13] have assigned structure (III), that now allocated to sandaracopimaric acid, to cryptopimaric acid.

Through the courtesy of Professor H. Imamura we have examined a small quantity (400 mg.) of cryptopimaric acid and have shown that it is a mixture. Hydrogenation of " cryptopimaric acid " furnishes " dihydrocryptopimaric acid " ($\nu_{max.}$ 824 cm.$^{-1}$; >C=CH–), from which a small quantity of dihydrosandaracopimaric acid was isolated. Isomerisation of " dihydrocroptopimaric acid " by toluene-*p*-sulphonic acid in benzene gives 7-allopimar-13(14)-en-15-oic acid (II) in high yield. The precursor of the acid (II) must be either dihydroisodextropimaric acid or the dihydro-derivative of Ukita's acid (IV).[14] Hence " cryptopimaric acid " is a mixture consisting predominantly of isodextropimaric and/or Ukita's acid (IV), together with smaller amounts of sandaracopimaric acid. The presence of other minor constituents could not be excluded.

Experimental.—Sandaracopimaric acid. Powdered sandarac resin (400 g.) was extracted by the method of Petru and Galik [3] to yield a gummy acid which was purified by chromatography on silica from benzene–ether (9 : 1). Thus obtained, sandaracopimaric acid separated from aqueous methanol in needles (1·1 g.), m. p. 170—171°, $[\alpha]_D^{19}$ −19·7° (Found: C, 79·1; H, 10·3. Calc. for $C_{20}H_{30}O_2$: C, 79·4; H, 10·0%). Petru and Galik [3] reported m. p. 173°.

Hydrogenation of sandaracopimaric acid (0·3 g.) in alcohol (25 ml.) containing palladium–charcoal (0·1 g.) occurred during 2 min., to yield dihydrosandaracopimaric acid, needles (from aqueous methanol) (0·2 g.), m. p. 176—178°, $[\alpha]_D^{19}$ +26·8° (Found: C, 78·7; H, 10·6. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·6%).

A solution of dihydrosandaracopimaric acid (0·1 g.) in chloroform (25 ml.) was saturated with hydrogen chloride at −5° during 4 hr. Purification of the semicrystalline product by chromatography on silica, from benzene–light petroleum (b. p. 60—80°) (1 : 1) gave 7-allopimar-13(14)en-15-oic acid [6] which separated from aqueous methanol in prisms (0·05 g.), m. p. and mixed m. p. 110° and having the requisite infrared absorption spectrum. This acid is dimorphous and occasionally separates from aqueous methanol in prisms, m. p. 129°. The isomorphs are readily interconvertible by seeding.

Cryptopimaric acid. The cryptopimaric acid supplied by Professor Imamura had m. p. 160—162°, $[\alpha]_D$ −20°. Attempts to achieve any separation by crystallisation and by chromatography were unsuccessful. Hydrogenation of cryptopimaric acid (0·2 g.) in alcohol (25 ml.) containing palladium–charcoal (0·05 g.) occurred during 2 min. to yield " dihydrocryptopimaric acid," m. p. 160—180°, $[\alpha]_D^{19}$ +18° (Found: C, 78·6; H, 10·5. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·6%). Chromatography of this acid (0·085 g.) from benzene, on silica, furnished dihydrosandaracopimaric acid (10 mg.), m. p. and mixed m. p. 176—178°, and having the requisite infrared absorption spectrum.

* After completion of this work we were informed by Dr. O. E. Edwards that he had reached the same conclusion by a different method. We thank Dr. Edwards for this information.

[7] Bose and Struck, *Chem. and Ind.*, 1959, 1628.
[8] Keimatsu, Ishiguro, and Fukuri, *J. Pharm. Soc. Japan*, 1937, **57**, 69.
[9] Hosking and Brandt, *Ber.*, 1935, **68**, 1313; Hosking, *New Zealand J. Sci. Tech.*, 1937, **19**, 208.
[10] Barton, " Progress in Organic Chemistry," Vol. I, p. 22, ed. Cook, 1952, Butterworths, London.
[11] Erdtman, " Chemistry of Carbon Compounds," Vol. IIB, p. 712, ed. Rodd, 1953, Elsevier, Amsterdam.
[12] Kondo, Imamura, and Suda, *Bull. Agric. Chem. Soc. Japan*, 1959, **23**, 233.
[13] Bruun, Ryhage, and Stenhagen, *Acta Chem. Scand.*, 1958, **12**, 789.
[14] Edwards and Howe, *Canad. J. Chem.*, 1959, **37**, 760.

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Isomerisation of " dihydrocryptopimaric acid " (0·30 g.) in benzene (10 ml.) containing toluene-*p*-sulphonic acid (0·05 g.), on the steam-bath during 1 hr. furnished 7-allopimar-13(14)-en-15-oic acid (0·2 g.), m. p. and mixed m. p. 110°, and having the requisite infrared absorption spectrum and specific rotation. No other homogeneous product could be isolated.

We thank Dr. O. E. Edwards, Ottawa, for a specimen of dihydropimaric acid and Professor Carl Djerassi, Stanford, for the rotatory dispersion measurement on dihydrosandaracopimaric acid.

Rotations refer to ethanol solutions and the infrared absorption spectra to CCl_4 solutions (Perkin-Elmer Model 21 spectrophotometer).

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158. *Fission of Triphenylmethyl Derivatives of Secondary Cellulose Acetates by Hydrogen Bromide.*

By W. R. D. LEIGH.

THE degree of substitution (D.S.) in secondary cellulose acetate normally required for good solubility in acetone is about ~2·3. Products in this range made by the conventional method of hydrolysing the triacetate have 30—50% of the free hydroxyl groups in the primary positions.

Previous attempts by Malm *et al.*[1] to prepare secondary cellulose acetates with all the free hydroxyl groups in the primary 6-positions *via* the 6-triphenylmethyl derivatives were unsuccessful owing to acetyl migration detritylation; the products had about 30% of the free hydroxyl groups in the primary positions and were similar to those obtained in the conventional way.

Using hydrogen bromide in anhydrous acetic acid as the detritylating agent we have found that acetyl migration can be suppressed and secondary cellulose acetates with up to 90% of the free hydroxyl groups in the primary positions prepared.

The general method was similar to that used by Malm *et al.* We prepared a starting compound containing 0·70 primary hydroxyl group per glucose unit by hydrolysing a textile-type cellulose acetate. This was tritylated and then reacetylated. Removing the trityl groups with hydrogen bromide at 0° gave a cellulose acetate of D.S. ~2·3. When higher temperatures were used for detritylation lower percentages of the free hydroxyl groups were in the primary position. The same was the case when water was present in the reaction medium, irrespective of the temperature of detritylation. Above 20° there was evidence of acetylation, during detritylation, from the acetic acid used as solvent and of degradation of the molecular chains.

For products containing less than 30% of the free hydroxyl groups in the primary positions it was found more convenient to acetylate a suitably hydrolysed starting compound directly up to D.S. ~2·3. In a slow, uncatalysed reaction with acetic anhydride at room temperature acetylation was predominantly on the primary hydroxyl groups and yielded products at D.S. ~2·3 with as little as 4% of the free hydroxyl groups in the primary positions. By varying the extent of initial hydrolysis and the conditions of reacetylation products were prepared covering the range 4—30% of free primary hydroxyl. Similarly preparations have been described by Malm *et al.*[2]

The use of hydrogen bromide extends the range of free-hydroxyl distributions which have been reported for secondary cellulose acetates and yields products with interesting solubility characteristics. Some properties of secondary cellulose acetates prepared in this

[1] Malm, Tanghe, and Laird, *J. Amer. Chem. Soc.*, 1948, **70**, 2740.
[2] Malm, Tanghe, Laird, and Smith, *J. Amer. Chem. Soc.*, 1954, **75**, 80.

way are given in the Table. The free-energy parameter, μ,[3] for the interaction of polymer and solvent, which previous work[4] has shown can be used to define the solubility of

Method of prep.	D.S.	Total OH	Primary OH	Primary OH (%)	$\overline{DP}_v$	$\overline{DP}_n$	μ (25°) $COMe_2$	μ (25°) CH_2Cl_2
HBr fission	2·33	0·67	0·58	87	170	145	0·29	0·66
	2·35	0·65	0·47	72	134	115	0·40	0·68
	2·35	0·65	0·25	38	124	110	0·42	0·62
Reactyln.	2·33	0·67	0·12	18	178	152	0·52	0·55
	2·33	0·67	0·09	13	167	143	0·54	0·53
	2·33	0·67	0·03	4	144	130	0·61	0·42
Starting material	2·33	0·67	0·32	48	192	162	0·41	0·63

From the nature of the theoretical derivation, μ would be expected to be nearly independent of molecular weight and concentration for a given solvent–polymer system. For acetone, μ was constant within $\pm 0{\cdot}01$ for five secondary cellulose acetate of D.S. ~2·3 and 40% primary hydroxyl over a $\overline{DP}_n$ range 100—158, suggesting that the variations obtained are indeed related to the hydroxyl distribution.

Infrared absorption at 2·5—15 μ by films cast from each product gave identical curves except for a slight change in the C–H stretching frequencies at 3·40 and 3·48 μ.

cellulose derivatives, varied with the free-hydroxyl distribution. For solutions in acetone it was lower the higher the amount of primary hydroxyl; the reverse held for methylene chloride.

Experimental.—Secondary cellulose acetate of D.S. ~2·3 in which 87% of the free hydroxyl groups were in the primary positions was prepared as follows:

Commercial textile-type cellulose acetate (D.S. 2·33, $\overline{DP}_v$ 192, $\overline{DP}_n$ 162) (100 g.) in which 48% of the free hydroxyl groups were in the primary positions was dissolved in glacial acetic acid (1 l.), and water (200 ml.) containing 36% hydrochloric acid (1·8 g.) was stirred in. The solution was left at 20° in a sealed jar until a sample isolated by precipitation in distilled water showed a primary hydroxyl content of 0·70 mol. per glucose unit, as estimated by the extent of tritylation under conditions employed by Malm *et al.*[5] Hydrolysis was complete in 460 hr. Then the solution was poured into distilled water (8 l.), and the precipitated product filtered off and washed acid-free. It was then dried in air at 60°. The product consisted of hard, horny particles which were ground in a micro-pulveriser to pass 20 mesh. 50 grams of this material (50 g.) were dissolved in anhydrous pyridine [containing <0·01% of water (Karl Fischer)] (250 ml.) at 70° in a sealed flask and then shaken. Triphenylmethyl chloride (60 g.) was added and dissolved by further shaking. The solution was kept at 70° for 24 hr. and the product isolated by dilution with acetone (400 ml.) and pouring the whole slowly into methanol (2 l.) with stirring. The precipitate was collected, washed free from triphenylmethyl chloride with methanol, and dried *in vacuo* over silica gel.

Analysis by sulphuric acid digestion[6] showed 0·69 trityl group per glucose unit.

The tritylated product (10 g.) was dissolved in anhydrous pyridine (50 ml.), and acetic anhydride (20 ml.) was added. The solution was left for 10 days at 25° in a sealed flask, and the product was then isolated by dilution with acetone and pouring into methanol as above. After the product had been washed free from acetic acid and acetic anhydride and dried *in vacuo* over silica gel analysis showed 0·69 trityl group and 2·30 acetyl groups per glucose unit.

The reactylated material (10 g.) was dissolved in anhydrous acetic acid (distilled over chromic oxide) (100 ml.) and stirred at 0°. A gel was formed but was broken up by the stirring. Anhydrous acetic acid (10 ml.), previously saturated with hydrogen bromide at 0°, was added and stirring continued. Within 5 min. the gel had liquefied and triphenylmethyl bromide began to separate. After 5 minutes' stirring the mixture was poured into methanol (2 l.). The precipitate was separated, washed free from bromide and acetic acid, and dried as above. Analysis gave: total OH 0·67, 0·66 group per glucose unit (D.S. 2·33); primary OH 0·58, 0·59 group per glucose unit; Ac 38·7, 38·6%; $\overline{DP}_v$ 170; $\overline{DP}_n$ 145.

[3] Huggins, *Ann. N.Y. Acad. Sci.*, 1942, **45**, 1; Flory, *J. Chem. Phys.*, 1942, **9**, 660; 1942, **10**, 51.
[4] Moore, *Chem. Age*, 1956, 255.
[5] Malm, Tanghe, and Laird, *Analyt. Chem.*, 1954, **26**, 188.
[6] Hearon, Hiatt, and Fordyce, *J. Amer. Chem. Soc.*, 1941, **63**, 3156.

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Analyses. Primary hydroxyl was estimated by the method of Malm *et al.*,[5,7] with sulphuric acid digestion [6] for the determination of triphenylmethyl. The method of Gardner and Purves [8] (toluene-*p*-sulphonyl chloride followed by iodination) was also used, with similar results.

The total hydroxyl content was estimated by isolating and weighing the carbanilate,[5] and the acetyl content by saponification.[9]

$\overline{DP}_v$ was evaluated from the intrinsic viscosity determined at the triacetate level by acetylation in 1 : 1 acetic anhydride–pyridine for 10 days at 25°. This procedure caused no degradation and the intrinsic viscosity was determined directly in the acetylation solvents. The relation $1{\cdot}02[\eta] = 8{\cdot}97 \times 10^{-5}[288\overline{DP}_v \times 0{\cdot}9012]^{0{\cdot}9}$ was used to derive $\overline{DP}_v$ from the intrinsic viscosity $[\eta]$. This relation held closely over a wide range. It has given values for $\overline{DP}_v$ which agree closely with those obtained by the relation derived by Phillip and Bjork [10] for cellulose acetates of D.S. ~2·3 and 40% primary hydroxyl content in acetone and has been confirmed by sedimentation studies.

$\overline{DP}_n$ was evaluated from the osmotic pressure in acetone or methylene chloride extrapolated to zero concentration.

The solvent–polymer free-energy parameter was determined from the slope of osmotic pressure–concentration plots. Where two-phase systems were obtained ($\mu > 0{\cdot}55$) the concentration and volume of the two phases were measured and μ obtained by equating Huggins's expression [11] for the activity of the polymer in each phase. In two samples of very low solubility the swelling of films was measured to obtain a value for μ.

C.S.R. Chemicals Pty. Ltd., 1 Mary Street,
Rhodes, Sydney, Australia. [*Received, August 8th*, 1960.]

[7] Malm, Tanghe, and Laird, *J. Amer. Chem. Soc.*, 1950, **72**, 2674.
[8] Gardner and Purves, *J. Amer. Chem. Soc.*, 1942, **64**, 1939.
[9] Malm, Genung, Williams, and Pile, *Ind. Eng. Chem., Analyt.*, 1944, **16**, 501.
[10] Phillip and Bjork, *J. Polymer Sci.*, 1951, **61**, 549.
[11] Huggins, "Cellulose and Cellulose Derivatives," Interscience Publ. Inc., New York, 1955, Part III, pp. 1115, 1200.

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159. 8-*Hydroxyquinoline Complexes of the Dibutyl- and Diphenyltin Radicals.*

By D. Blake, G. E. Coates, and J. M. Tate.

Most compounds containing di-n-butyltin and diphenyltin groups are relatively low melting and too soluble in organic solvents for easy purification. The 8-hydroxyquinoline derivative, $R_2Sn(C_9H_6NO)_2$, is in both cases easy to prepare and to purify, and serves as a convenient compound for characterization.

Experimental.—8-Hydroxyquinoline (2 mol.) in ethanol was added to di-n-butyltin dichloride (1 mol.) in ethanol. The dioxine *derivative* is precipitated on addition of sodium acetate in aqueous ethanol, followed by a little aqueous ammonia. Crystallization from ethanol or light petroleum (b. p. 80—100°) gives yellow plates, m. p. 154·5—155·5° (Found: C, 59·6; H, 5·8. $C_{26}H_{30}N_2O_2Sn$ requires C, 59·9; H, 5·8%).

Diphenyltin di-(8-hydroxyquinolinate), similarly prepared from diphenyltin dibromide, forms yellow plates, m. p. 231—233° (from ethanol) (Found: C, 64·3; H, 3·9. $C_{30}H_{22}N_2O_2Sn$ requires C, 64·3; H, 3·9%).

Dichlorodi-n-butyl-(2,2′-bipyridyl)tin is immediately precipitated when 2,2′-bipyridyl (1 mol.) in ethanol is added to di-n-butyltin dichloride (1 mol.) in the same solvent, and crystallizes from ethanol or light petroleum (b. p. 80—100°) as colourless needles, m. p. 179·5—180° (Found: C, 46·9; H, 5·9. $C_{18}H_{26}Cl_2N_2Sn$ requires C, 47·0; H, 5·7%).

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South Road, Durham. [*Received, September 1st*, 1960.]

160. *Further Studies on the Preparation of Symmetrical Pinacols by Cathodic Reduction.*

By M. J. Allen, M. Cohen, W. G. Pierson, and (Miss) J. A. Siragusa.

We here report the electrochemical preparation of some new pinacols in yields which, though often poor owing to the instability of the starting material in the electrolysis medium, are yet better than can be obtained by the usual chemical methods. Although 4-aminoacetophenone forms its pinacol [1] quite readily, 3-aminoacetophenone apparently decomposes too rapidly in the medium. However, electrolysis of 3-acetamidoacetophenone does give the corresponding pinacol. It was possible to obtain some pinacol from the rather unstable 3-amino-4-methoxyacetophenone, but cathodic reduction of the acetylated ketone gave a better yield.

Experimental.—The electrolytic cells as well as the Redoxotrol used for the controlled potential reductions have been described previously.[2] A porous membrane separated the mercury cathode from the platinum anode. The reference potentials used were obtained from voltametric curves obtained under conditions identical with those used preparatively. The experimental data are given in the Table.

3-Amino-4-methoxyacetophenone and 3-acetyl-6-methylpyridine were obtained from the Aldrich Chemical Company, Milwaukee, Wisc., U.S.A. 3-Acetamidoacetophenone,[3] 3-acetamido-4-methoxyacetophenone,[4] ω-dimethylaminoethyl-4-methoxyacetophenone,[5] and 3-propionylpyridine [6] were prepared by published methods. The 3-acetyl-6-dimethylaminopyridine, prepared by reaction of 3-acetyl-6-chloropyridine [7] with dimethylamine, was kindly supplied by Dr. G. Walker of our laboratories.

Isolation of pinacols. (*a*) The catholyte was evaporated to a small volume under reduced pressure, then refrigerated, and the gum which separated was washed with water, dissolved in a minimum quantity of acetone, filtered, and treated with a large excess of ether. The precipitate was collected, triturated with ether, and recrystallized from acetone, giving 2,3-*di*-m-*acetamidophenylbutane*-2,3-*diol* (1·01 g.), m. p. 265·5—267·5° (decomp.) (Found: C, 67·1; H, 6·95; N, 7·7. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8; N, 7·9%).

(*b*) The filtered catholyte was made basic with a saturated solution of potassium carbonate, and the resulting yellow solid separated by decantation and extracted a number of times with methylene chloride. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was triturated with cold anhydrous ethanol, and the solid which was formed crystallized from 50% ethanol (charcoal). Recrystallization from ethanol–ether yielded the 2,3-*di*-(3-*amino*-4-*methoxyphenyl*)*butane*-2,3-*diol* (0·27 g.), m. p. 201—202° (Found: C, 64·7; H, 7·4; N, 8·2. $C_{18}H_{24}N_2O_4$ requires C, 65·0; H, 7·3; N, 8·4%).

(*c*) The residue obtained on evaporation of the catholyte was taken up in methylene chloride. The solution was dried (Na_2SO_4), filtered, and diluted with an excess of pentane. The precipitate crystallized from methylene chloride–pentane and then from ethyl acetate to yield 2,3-*di*-(3-*acetamido*-4-*methoxyphenyl*)*butane*-2,3-*diol* (1·02 g.), m. p. 176—178° (Found: C, 63·6; H, 7·0; N, 6·5. $C_{22}H_{28}N_2O_6$ requires C, 63·4; H, 6·8; N, 6·7%).

(*d*) The catholyte was evaporated under reduced pressure below 40° and the yellow oil obtained dissolved in isopropyl alcohol (200 ml.). This solution upon dilution with an excess of ether gave a gummy yellow solid which was washed with ether, dried, and then dissolved in water. This solution was made basic and the precipitate extracted with ether. After evaporation of the dried ether extracts the residue was triturated with pentane to yield a white powder which, on crystallization from ether, gave 1,6-*bisdimethylamino*-3,4-*di*-p-*methoxyphenylhexane*-3,4-*diol* (13·4 g.), m. p. 161° (Found: C, 69·5; H, 8·7; N, 6·85. $C_{24}H_{36}N_2O_4$ requires C, 69·2; H, 8·7; N, 6·7%).

[1] Allen and Corwin, *J. Amer. Chem. Soc.*, 1950, **72**, 114.
[2] Allen, "Organic Electrode Processes," Chapman and Hall, London, 1958, pp. 24—28, 33—39; *Canad. J. Chem.*, 1959, **37**, 257.
[3] Rupe, Braun, and von Zembruski, *Ber.*, 1901, **34**, 3523.
[4] Bogert and Curtin, *J. Amer. Chem. Soc.*, 1923, **45**, 2164.
[5] Mannich and Lammering, *Ber.*, 1922, **55**, 3518.
[6] Engler, *Ber.*, 1891, **24**, 2539.
[7] Räth and Schiffmann, *Annalen*, 1931, **487**, 127.

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(*e*) Water (40 ml.) was added to the catholyte and the basicity adjusted to pH 8 with dilute hydrochloric acid. The mixture was saturated with sodium chloride and extracted with methylene chloride, and the extracts were dried and evaporated under reduced pressure. The residue, on trituration with ethyl acetate, gave *3,4-di-3′-pyridylhexane-3,4-diol* (1·2 g.), m. p. 188—189° (from aqueous methanol) (Found: C, 70·3; H, 7·4; N, 10·6. $C_{16}H_{20}N_2O_2$ requires C, 70·55; H, 7·4; N, 10·3%).

(*f*) The yellow solid formed on evaporation of the catholyte under reduced pressure was triturated with a small quantity of 5% ethanol and left at room temperature overnight. The precipitate was collected and recrystallized from aqueous ethanol, giving *2,3-bis-(6-dimethylamino-3-pyridyl)butane-2,3-diol* (1·73 g.), m. p. 247—248° (Found: C, 65·6; H, 8·0; N, 16·9. $C_{18}H_{26}N_4O_2$ requires C, 65·4; H, 7·9; N, 16·95%).

(*g*) The crystalline precipitate formed during the reaction was filtered off from the catholyte

Catholyte	(*a*) 3-NHAc·C_6H_4·COMe (15 g.) EtOH (90 ml.) H_2O (33·6 ml.) KOAc (40·5 g.)	(*b*) 3-NH_2-4-MeO·C_6H_4·COMe (3·9 g.) Conc. HCl (3·9 ml.) H_2O (46·1 ml.)
Anolyte	40% K_2CO_3	Conc. HCl (3·9 ml.), H_2O (46·1 ml.)
Cathode area (cm.²)	52	20·5
Ref. pot. *vs.* S.C.E. (v)	−1·60	−1·10
Electrolysis temp.	81·5° (b. p.)	20—25°
Initial amperage	5·8	3·5
Final amperage	0·5	0·25
Initial applied voltage	13·5	8·0
Final applied voltage	3·5	3·9
Electrolysis time (min.) to current plateau	73	32
Coulombs passed	9212 (112%)	2084 (91·4%)
Yield (%)	6·7	6·9

Catholyte	(*c*) 3-NHAc-4-MeO·C_6H_4·COMe (3·0 g.) EtOH (25 ml.) 2N-KOH (25 ml.)	(*d*) 4-MeO·C_6H_4·CO·CH_2·CH_2·NMe_2,HCl (138 g.) Conc. HCl (23 ml.) H_2O (897 ml.)
Anolyte	N-KOH	Conc. HCl (2 ml.), H_2O (78 ml.)
Cathode area (cm.²)	20·5	111·3
Ref. pot. *vs.* S.C.E. (v)	−2·0	−1·36
Electrolysis temp.	30°	27—29°
Initial amperage	4·1	7·4
Final amperage	0·04	0·9
Initial applied voltage	17·0	15·0
Final applied voltage	2·5	5·1
Electrolysis time (min.) to current plateau	61	270
Coulombs passed	1522 (108%)	60,190 (110%)
Yield (%)	33·3	11·4

Catholyte	(*e*) 3-C_5H_4N·COEt (6 g.) EtOH (7·5 ml.) 1·5N-KOH (22·5 ml.)	(*f*) 6-Me_2N·C_5H_3N·COEt-3 (6 g.) EtOH (30 ml.) 2N-KOH (30 ml.)	(*g*) 6-Me·C_5H_3N·COMe-3 (3·9 g.) Conc. HCl (3·9 ml.) H_2O (46·1 ml.)
Anolyte	1·5N-KOH–EtOH (3 : 1)	40% K_2CO_3	Conc. HCl (3·9 ml.), H_2O (46·1 ml.)
Cathode area (cm.²)	16	20·5	20·5
Ref. pot. *vs.* S.C.E. (v)	−1·60	−1·90	−1·10
Electrolysis temp.	40°	25°	25°
Initial amperage	5·5	6·0	3·5
Final amperage	0·55	0·15	0·25
Initial applied voltage	19·0	41·7	8·0
Final applied voltage	5·0	3·8	3·9
Electrolysis time (min.) to current plateau	31	88	32
Coulombs passed	3828 (89·3%)	4196 (119·3%)	2084 (91·4%)
Yield (%)	19·8	28·8	63·8

after refrigeration. On being washed with ethanol–ethyl acetate (1 : 1) and recrystallized from ethanol it gave 2,3-*di*-(6-*methyl*-3-*pyridyl*)*butane*-2,3-*diol* (4·37 g.), m. p. 218—219° (Found: C, 70·2; H, 7·4; N, 9·9. $C_{16}H_{20}N_2O_2$ requires C, 70·55; H, 7·4; N, 10·3%).

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161. *Quaternary Derivatives of 2,2′-Pyridil Dioxime and of 2,2′-Bipyridyls.*

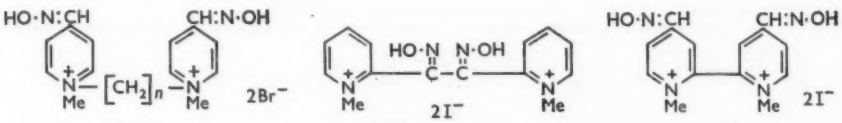
By MARY PITMAN and P. W. SADLER.

4-MONOXIMES and 4,4′-dioximes of polymethylene-1,1′-di(pyridinium bromide) (I; $n = 1$—5) are potent reactivators of diethyl and di-*O*-isopropylphosphorylacetocholinesterases.[1,2] Bonding of the quaternary ammonium groups to two sites of the enzyme surface has been postulated to explain the high activity,[2] and the finding that the trimethylene derivative (I; $n = 3$) has the highest activity indicates that these two points of attachment are separated by a distance not exceeding 5 Å. To obtain further information concerning the intersite distance, potential reactivators with more rigid structures were investigated, namely, compounds of type (II) and (III) containing C_4 and C_2 links respectively between the nitrogen atoms.

A dioxime of 2,2′-pyridil has been described,[3] but this seems to have been a mixture as two dioximes and a monoxime were obtained by us on reaction of hydroxylamine with 2,2′-pyridil. The three oximes were quaternized by the action of methyl iodide in nitrobenzene.

The action of freshly sublimed selenium dioxide on 4,4′-dimethyl-2,2′-bipyridyl under various conditions gave a mixture of products including the 4,4′-dicarboxy-, 4-carboxy-4′-methyl, and 4-carboxy-4′-formyl derivative in addition to the dialdehyde which was obtained only in small yield. Although 2,2′-bipyridyl[4] and 4,4′-dimethyl-2,2′-bipyridyl were quaternized by the action of methyl iodide in a sealed tube, the dimethiodide (III) was not obtained from the dioxime.

The quaternary dioximes (II) have reactivating properties similar to that of pyridine-2-aldoxime methiodide.



(I) (II) (III)

Experimental.—*2,2′-Pyridil oximes.* 2,2′-Pyridil (0·3 mole) was heated with hydroxylamine (0·6 mole) in ethanol (1 l.) containing sodium (1·5 g.) for 1 hr. The reaction mixture was filtered and reduced to 200 c.c. before the addition of hot water (300 c.c.), which precipitated material (41 g.), m. p. 228°, containing three components. A 2,2′-*pyridil dioxime* (4·8%), m. p. 246°, was sparingly soluble in hot ethanol and was recrystallized to constant m. p. from 50% aqueous ethanol (Found: C, 59·4; H, 4·2; N, 23·3. $C_{12}H_{10}N_4O_2$ requires C, 59·5; H, 4·1; N, 23·1%). A 2,2′-*pyridil dioxime* (28%), m. p. 235°, was obtained pure after several recrystallizations from ethanol (Found: C, 59·5; H, 4·1; N, 22·8%). Concentration of these liquors

[1] Hobbiger, O'Sullivan, and Sadler, *Nature*, 1958, **182**, 1498; Hobbiger and Sadler, *Nature*, 1958, **182**, 1672; Hobbiger and Sadler, *Brit. J. Pharmacol.*, 1959, **14**, 192.
[2] Hobbiger, Pitman, and Sadler, *Biochem. J.*, 1960, **75**, 363.
[3] Mathes, Sauermilch, and Klein, *Chem. Ber.*, 1951, **84**, 452; Blau, *Monatsh.*, 1889, **10**, 382.
[4] Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2527.

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and the addition of water gave a *monoxime* (1·4%), m. p. 207° (from ethanol) (Found: C, 63·2; H, 4·1; N, 18·5. $C_{12}H_9N_3O_2$ requires C, 63·4; H, 4·0; N, 18·5%). Mathes *et al.*[3] described a dioxime, m. p. 215°; no analysis was given.

The dioxime of m. p. 235° (5 g.) was heated in nitrobenzene (100 c.c.) with a two-fold excess of methyl iodide under reflux for 18 hr. After cooling, the nitrobenzene was decanted from an oil. Several crystallisations from methanol gave the *dimethiodide* as yellow needles, m. p. 259° (Found: C, 32·0; H, 3·4; N, 10·5; I, 48·2. $C_{14}H_{16}I_2N_4O_2$ requires C, 31·9; H, 3·1; N, 10·7; I, 48·3%). The dioxime of m. p. 246° similarly gave a *dimethiodide*, m. p. 274° (Found: C, 32·1; H, 3·1; I, 49·0%). The *monoxime dimethiodide* had m. p. 193° (Found: C, 33·5; H, 2·8; I, 49·6. $C_{14}H_{15}I_2N_3O_2$ requires C, 32·9; H, 2·9; I, 49·7%).

4,4′-Dimethyl-2,2′-bipyridyl. This base was obtained as plates (from benzene), m. p. 171°, by Case's method.[4] In the reaction of 2-bromo-4-methylpyridine with copper powder, concentrated hydrochloric acid was used for extraction of the mixture to achieve the reported yield (33%).

Oxidation of 4,4′-dimethyl-2,2′-bipyridyl. Reactions were carried out on 0·02 molar scale. 4,4′-Dimethyl-2,2′-bipyridyl, intimately mixed with freshly sublimed selenium dioxide, was gently heated. A vigorous reaction ensued, the temperature rising to 130°. The mixture was kept at 120° for ½ hr., then extracted with 17% hydrochloric acid. No ketonic compound was isolated from the neutralised extract. *4′-Methyl-2,2′-bipyridyl-4-carboxylic acid* was obtained in a similar experiment in which the mixture was extracted with boiling isopentyl acetate (Found: C, 67·6; H, 4·8; N, 13·1. $C_{13}H_{10}N_2O_2$ requires C, 67·3; H, 4·7; N, 13·1%). The same product was obtained when the reactants were heated under reflux in glacial acetic acid for ½ hr.; heating for longer periods produced 2,2′-bipyridyl-4,4′-dicarboxylic acid. No reaction occurred when the reactants were heated under reflux in ethyl acetate for ½ hr. but when isopentyl acetate was used, 200 mg. of the *4,4′-dialdehyde* were obtained (Found: C, 67·8; H, 4·1; N, 13·5. $C_{12}H_8N_2O_2$ requires C, 67·9; H, 3·8; N, 13·2%) together with unchanged starting material; the dialdehyde gave a *dioxime*, m. p. 277° (Found: C, 59·8; H, 4·3; N, 23·3. $C_{12}H_{10}N_4O_2$ requires C, 59·5; H, 4·1; N, 23·1%). Heating under reflux for longer periods gave *4′-formyl-2,2′-bipyridyl-4-carboxylic acid* as the major product (Found: C, 63·2; H, 3·5; N, 11·7. $C_{13}H_8N_2O_3$ requires C, 63·2; H, 3·5; N, 12·3%) [*2,4-dinitrophenylhydrazone* (Found: C, 52·9; H, 2·9; N, 20·8. $C_{18}H_{13}N_6O_6$ requires C, 52·9; H, 2·7; N, 20·6%).

1,1′,4,4′-Tetramethyl-2,2′-bipyridylium di-iodide. 4,4′-Dimethyl-2,2′-bipyridyl (1 g.) was heated in methanol (5 c.c.) with methyl iodide (2 c.c.) at 100° for 10 hr. in a sealed tube. From methanol the *dimethiodide* formed lemon-yellow crystals, m. p. 279° (Found: C, 36·1; H, 3·9; I, 53·9. $C_{14}H_{18}I_2N_2$ requires C, 35·9; H, 3·9; I, 54·3%).

The three acids and the aldehyde did not melt below 320°.

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162. *A Simple Route to 4,5-Diamino-2-hydroxypyrimidine.*

By ABRAHAM KALMUS and FELIX BERGMANN.

4,5-DIAMINO-2-HYDROXYPYRIMIDINE is the key compound for the synthesis of 2-hydroxypurine and 8-substituted derivatives. Until now, it has been prepared by reduction of 5-nitrocytosine.[1] The recent finding that 4,5-diaminouracil is converted by phosphorus pentasulphide selectively into the 6-thione,[2] opened a new approach by catalytic desulphuration. This reaction proceeded with satisfactory yield in N-sodium hydroxide. 4,5-Diamino-2-hydroxypyrimidine can be isolated conveniently as the sulphate.

Previous experience has shown that desulphuration of a methylthio-derivative requires

[1] Johns, *Amer. Chem. J.*, 1911, **45**, 82.
[2] Levin, Kalmus, and Bergmann, *J. Org. Chem.*, 1960, **25**, 1752.

less drastic conditions than that of the parent thione and thus results in higher yields.[3] The 6-methylthio-pyrimidine was very sensitive to alkali, and reaction with Raney nickel was carried out in an aqueous suspension. The yield of 4,5-diamino-2-hydroxypyrimidine was slightly higher than that obtained by direct desulphuration of the 6-thione. However, the overall yield of diaminohydroxypyrimidine from diaminouracil was greater by the latter route.

Condensation of 4,5-diamino-2-hydroxypyrimidine sulphate with urea leads quantitatively to 2,8-dihydroxypurine. Similar high yields have been obtained by Johns[1] in the cyclisation of the diaminohydroxypyrimidine to 2-hydroxypurine.

Experimental.—*4,5-Diamino-2-hydroxypyrimidine sulphate.* A solution of 4,5-diamino-2-hydroxy-6-mercaptopyrimidine sulphate[2] (2·2 g., 0·01 mole) in N-sodium hydroxide (20 ml., 2 equiv.) was refluxed with vigorous stirring for 2 hr., in the presence of Raney nickel (2 g.). The catalyst was removed and the filtrate acidified with 10% sulphuric acid, producing 4,5-diamino-2-hydroxypyrimidine sulphate monohydrate[1] (1·65 g., 67%). Recrystallization from 10% sulphuric acid gave white prisms, decomposing above 300°.

4,5-Diamino-2-hydroxy-6-methylthiopyrimidine. A mixture of the 6-mercaptopyrimidine sulphate (2·2 g., 0·01 mole), 0·5N-sodium hydroxide (40 ml.), and methyl iodide (2 ml.) was stirred at room temperature for 1 hr. The precipitate crystallised from water in yellowish needles (1·3 g., 74%) which decomposed at about 260° (Found: C, 35·0; H, 4·5. Calc. for $C_5H_8N_4OS$: C, 34·9; H, 4·65%): $\lambda_{max.}$ at pH 2·5, 320—321 mμ; at pH 8·0, 312—313 mμ.

For desulphuration, a suspension of 4,5-diamino-2-hydroxy-6-methylthiopyrimidine (1·7 g.; 0·01 mole) and Raney nickel (2 g.) in 100 ml. of water was stirred at 80—85° for 1 hr. The filtrate was concentrated *in vacuo*. The crystals (0·95 g.; 75%) deposited overnight were recrystallised from 10% sulphuric acid, producing white prisms of 4,5-diamino-2-hydroxypyrimidine sulphate monohydrate (see above).

2,8-Dihydroxypurine. An intimate mixture of the diaminohydroxypyrimidine (0·24 g.) and urea (0·2 g.) was heated to 195° during 20 min. The cake was dissolved in ammonia solution (10%; 6 ml.), the solution decolorised with charcoal, and the filtrate acidified with glacial acetic acid. Short needles (0·15 g., 100%), decomposing above 300°, were obtained; $\lambda_{max.}$ at pH 8·0, 263 and 306 mμ.[4] The compound was chromatographically pure.

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Department of Pharmacology, The Hebrew University,
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[3] Kalmus and Bergmann, *J.*, 1960, 3679.
[4] Mason, *J.*, 1954, 2071.

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163. *Deamination of Cyclohexylamine by* [^{18}O]*Nitrous Acid.*

By D. L. Boutle and C. A. Bunton.

Streitweiser and Schaeffer[1] have shown that the deamination of optically active [2-^{2}H]cyclohexylamine proceeds with retention of configuration. This observation suggests that the life of the intermediate carbonium ion is less than that required for interconversion of the cyclohexane ring.[2] Another possible reaction path, which would give retention of configuration, is an S_Ni decomposition of an intermediate such as the hypothetical diazo-hydroxide (I) or its conjugate acid.

This reaction path has been excluded, for deamination in water, by the use of [^{18}O]-nitrous acid. The difficulty in this type of experiment is that nitrous acid readily exchanges its oxygen with water. Provided that deamination is under conditions such that the predominant exchange path is the slow formation, and subsequent hydration, of dinitrogen

[1] Streitweiser and Schaeffer, *J. Amer. Chem. Soc.*, 1959, **81**, 4275.
[2] Dauben, Tweit, and Hannerkautz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420.

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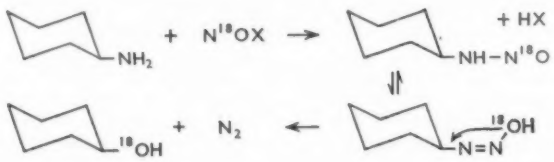
trioxide, it is possible for attack of the amine on the latter to be faster than that of water: [3]

$2HNO_2 \rightleftharpoons H_2O + N_2O_3 \xrightarrow{R\cdot NH_2}$ Products. This experiment has already been done with aniline, which suppressed the exchange of nitrous acid by trapping dinitrogen trioxide as fast as it was formed.[3]

We have now done a similar experiment with cyclohexylamine and find that it is possible partially to suppress the exchange of the nitrous acid. The cyclohexanol isolated



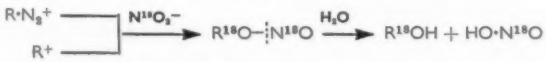
(I)

from this deamination had more than 90% of its oxygen derived from the water, and there was only 30% of exchange of oxygen between nitrous acid and water. Therefore the absence of oxygen derived from the nitrous acid was not an artefact of an exchange with water.

Isotopic abundances of cyclohexanol.

Isotopic abundance (atom % excess): $NaNO_2$ 0·97, 0·86; ROH 0·08, 0·08.

The small amount of tracer in the cyclohexanol (see above) could have come from the reaction between the carbonium (or diazonium) ion and the nitrite ion:



This reaction should also exchange an oxygen atom between water and nitrous acid; another route for this exchange is: [4]

$$RO\dot{}H + HO-\dot{}NO \rightleftharpoons RO-\dot{}NO + H_2O$$

The deamination of [2-^{2}H]cyclohexylamine was in aqueous acetic acid,[1] whereas we used water as solvent. This was because nitrosyl acetate reacts more readily with water than with amines, and if it were present it would be difficult to suppress the oxygen exchange of the nitrous acid.[3,5] However it is unlikely that such a change of solvent could affect the whole nature of the deamination.

Experimental.—Cyclohexylamine (10 g.) was dissolved in isotopically normal water (60 c.c.) containing sodium [^{18}O]nitrite [6] (20 g.). (For the control test on the exchange, 7 g. of sodium nitrite were used.) 2M-Sulphuric acid was added dropwise with vigorous stirring at *ca.* 25°. The pH was measured with a Cambridge pH meter. The initial value of pH was *ca.* 9, and the rate of addition of acid was regulated so that it never fell below 6. (After the theoretical amount of sulphuric acid had been added the pH fell sharply.) The reaction required several hours for completion. The solution was then warmed to 40° with excess of alkali to hydrolyse any cyclohexyl nitrite present; [4] this heating was omitted from the control experiment on the exchange of nitrous acid.

The cyclohexanol was isolated by Streitweiser and Schaeffer's method [1] (extraction with ether from a solution saturated with sodium chloride). The crude cyclohexanol was purified by gas–liquid chromatography on a Silicone oil–Celite column. The isotopic abundance of the cyclohexanol was determined by equilibration with carbon dioxide.[7] For the control test

[3] Bunton and Masui, *J.*, 1960, 304.
[4] Allen, *J.*, 1954, 1968.
[5] Anbar and Taube, *J. Amer. Chem. Soc.*, 1955, **77**, 2993.
[6] Bunton, Llewellyn, and Stedman, *J.*, 1959, 568.
[7] Dahn, Moll, and Menassé, *Helv. Chim. Acta*, 1959, **42**, 1224.

on the exchange of nitrous acid, in the presence of cyclohexylamine, the isotopic abundance of the sodium nitrite was determined by Anbar and Taube's method.[5]

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164. *An Enzymic Resolution of Serine.*

By LEO BENOITON.

IN the case of serine, the Greenstein enzymic procedure [1] for the resolution of amino-acids is not entirely satisfactory because the required substrate, *N*-chloroacetylserine, cannot be obtained in good yield. The need for optically active serine in this laboratory has induced a search for a more satisfactory preparation of this derivative, or, alternatively, for some other substrate.

N-Chloroacetylserine was prepared directly by the activated ester method [2] using *p*-nitrophenyl chloroacetate, and indirectly, by an *O* ⟶ *N*-acyl shift, from *O*-chloroacetylserine in basic solution, but neither method gave the desired yield. The *O*-chloroacetylserine was obtained by reverse esterification of serine by molten chloroacetic acid saturated with hydrogen chloride.

A satisfactory resolution was achieved by using the acetyl derivative as substrate.[3] *N*-Acetyl-DL-serine was prepared from DL-serine by the *O* ⟶ *N*-acyl shift [4] applied to *O*-acetyl-DL-serine [5] and was resolved without isolation of any of these intermediates, to give L- and D-serine in yields of 70 and 60% respectively. The overall procedure was such that it is readily applicable to both small and large quantities.

Another interesting application of the *O* ⟶ *N*-acyl shift was the preparation of *N*-glycylserine from *O*-chloroacetylserine hydrochloride in methanolic ammonia.

Experimental.—*N-Chloroacetyl-*DL*-serine.* (*a*) Activated ester method. Chloroacetyl chloride (2·25 g.) was added to the sodium salt of *p*-nitrophenol (3·2 g.) in ethyl acetate, and the suspension was warmed until the orange colour had disappeared (5 min.). The mixture was cooled and filtered, the filtrate evaporated, and the residue crystallised from benzene, to give *p*-nitrophenyl chloroacetate (3·3 g., 70%), m. p. 95° (lit.,[6] 94°). This ester (1·57 g.) in ethyl acetate (15 ml.) was added to DL-serine (0·5 g.) and sodium hydrogen carbonate (0·63 g.) in water in an open vessel, and the mixture was stirred vigorously for 18 hr. The precipitate of *p*-nitrophenol was filtered off, and the filtrate washed with ethyl acetate, acidified, and saturated with sodium chloride and finally exhaustively extracted with ethyl acetate. The ethyl acetate was dried, the solvent removed under a vacuum, and the residue triturated with light petroleum; filtration and recrystallisation from ethyl acetate, gave the *N*-chloroacetyl derivative (0·4 g., 45%), m. p. 123° (lit.,[7] m. p. 122—123°).

(*b*) By *O* ⟶ *N*-acyl shift. DL-Serine (8·4 g.) was dissolved in molten chloroacetic acid (50 g.), and a slow stream of hydrogen chloride was passed through the solution, kept at 65—70°, for 8 hr. The solution was allowed to cool and ether (150 ml.) was added gradually as crystallisation occurred. The solid was filtered off, washed with ether, and redissolved in hot chloroacetic acid, and the whole operation was then repeated twice. Recrystallisation of the final product from glacial acetic acid gave, after washing with ether, the slightly hygroscopic *O-chloroacetyl-*DL*-serine hydrochloride* (10·5 g., 60%), m. p. 147—148°. A sample for analysis

[1] Greenstein, *Adv. Protein Chem.*, 1954, **9**, 121.
[2] Bodansky, *Acta Chim. Acad. Sci. Hung.*, 1957, **10**, 335.
[3] Akabori, Otani, Marshall, Winitz, and Greenstein, *Arch. Biochem. Biophys.*, 1959, **83**, 1.
[4] Narita, *Biochim. Biophys. Acta*, 1958, **30**, 352.
[5] Sheehan, Goodman, and Hess, *J. Amer. Chem. Soc.*, 1956, **78**, 1367.
[6] Auwers, Baum, and Lorenz, *J. prakt. Chem.*, 1927, **115**, 81.
[7] Fischer and Roesner, *Annalen*, 1910, **375**, 199.

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was dried under a vacuum at 78° (Found: C, 27·5; H, 4·2; N, 6·3. $C_5H_9Cl_2NO_5$ requires C, 27·5; H, 4·2; N, 6·4%).

To samples of this *O*-acyl derivative, dissolved in water, were added N-sodium hydroxide, N-ammonia, and triethylamine until the solutions remained basic to Methyl Red. After 2 hr. the solutions were acidified and the *N*-chloroacetyl-DL-serine was isolated by extraction with ethyl acetate as described above. Yields of 30—45% were obtained.

Resolution of DL-*serine.* A suspension of DL-serine (4·2 g.) in anhydrous acetic acid (100 ml.) was saturated with hydrogen chloride at room temperature. Within a few minutes the serine had dissolved, after which the *O*-acetyl derivative began to crystallise. Next day, the precipitate (5·9 g., 80%; containing only a trace of serine) was collected and washed with ether, and the filtrate and washings were evaporated to dryness. The precipitate and residue were recombined (the filtration was found more convenient than evaporation of the reaction mixture) and dissolved in water (40 ml.), and N-ammonia was added until the solution remained basic to litmus. After 30 min. (the $O \longrightarrow N$ shift is practically instantaneous) the solution was placed under a vacuum to remove excess of ammonia, and passed through a column (50 ml. burette) of Amberlite IR-120 (H^+ form) which was subsequently washed with water. That portion of the eluate which was acid to Congo Red was brought to pH 7·5 with ammonia, 30 mg. of acylase I[8] were added, and the solution was kept at 37° for 16 hr. An additional 5 mg. of enzyme were then added and the digestion was allowed to continue a further 8 hr. The digest was brought to pH 5·2 with acetic acid, treated with charcoal, and filtered, the filtrate was concentrated, and ethanol (5 vols.) was added. After several hours' cooling, the L-serine (1·37 g.) was collected. The mother-liquor was freed from ethanol under a vacuum, the remaining solution was passed through the regenerated Amberlite IR-120 column, and the column was eluted first with water and then with N-ammonia. Evaporation of the ammonia eluate gave a second crop (0·25 g.) of the L-isomer. Recrystallisation of the combined products from water–ethanol afforded L-serine (1·47 g., 70%), $[\alpha]_D^{25}$ +14·3° (*c* 2 in N-hydrochloric acid) (lit.,[8] $[\alpha]_D^{25}$ +15·1°) (Found: N, 13·1. Calc. for $C_3H_7NO_3$: N, 13·3%).

The aqueous eluate (acid to Congo Red), which was obtained before the elution with ammonia, was concentrated and then refluxed in 2N-hydrochloric acid for 2 hr. The hydrolysate was evaporated to dryness, the residue taken up in water, the solution brought to pH 5·7 with pyridine, and the amino-acid precipitated with ethanol. Recrystallisation from water–ethanol gave D-serine (1·26 g., 60%), $[\alpha]_D^{25}$ −14·4° (*c* 2 in N-hydrochloric acid) (lit.,[9] $[\alpha]_D^{25}$ −15·0°) (Found: N, 13·1%).

A small amount of DL-serine (4%) was recovered by eluting the resin column with aqueous ammonia after the first resin treatment prior to the digestion.

*N-Glycyl-*DL-*serine.* A solution of *O*-chloroacetyl-DL-serine hydrochloride (0·5 g.) in methanol (25 ml.) was saturated with ammonia and left at 23° for 3 days. The solution was concentrated to a small bulk, then cooled, and the crystals were collected and washed by suspension in methanol. Recrystallisation from water–ethanol gave the dipeptide (0·25 g., 60%) (Found: N, 17·2. Calc. for $C_5H_{10}N_2O_4$: N, 17·3%) which was chromatographically indistinguishable from an authentic sample prepared from *N*-chloroacetyl-DL-serine.[9]

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[8] Birnbaum, Levintow, Kingsley, and Greenstein, *J. Biol. Chem.*, 1952, **194**, 455.
[9] Rao, Birnbaum, Kingsley, and Greenstein, *J. Biol. Chem.*, 1952, **198**, 507.

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